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The American Journal of Medicine

VOL. VIII FEBRUARY, 1950 No. 2

Editorial

Clinical Studies

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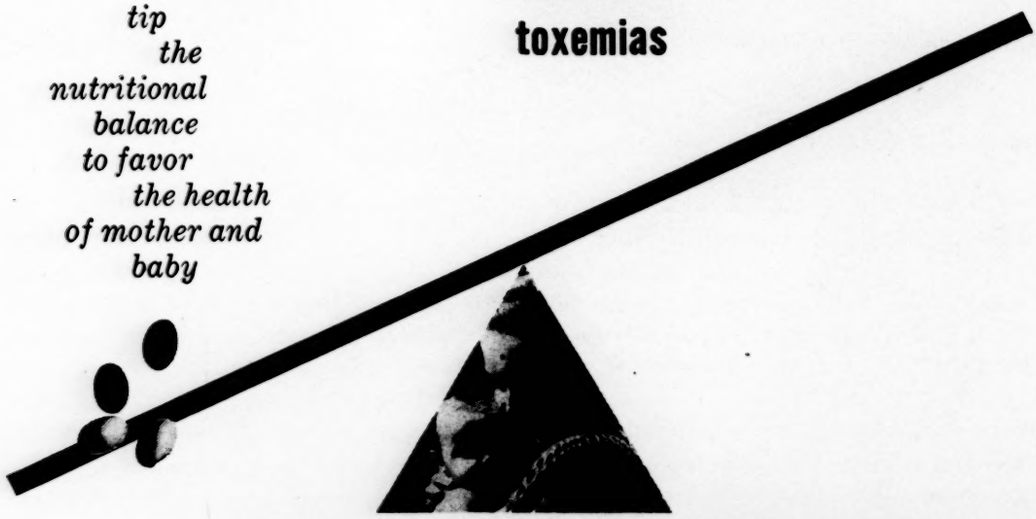
better nutrition means

fewer: **stillbirths**
neonatal deaths
complications of delivery
pre-eclampsias
abortions
toxemias

tip the nutritional balance to favor the health of mother and baby



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. . . specially designed to help meet increased vitamin-mineral needs during pregnancy and lactation. Improved maternal nutrition means better physical health for the mother with many prenatal symptoms and discomforts almost wholly relieved or avoided, and sturdier babies with greater resistance to disease.

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The American Journal of Medicine

VOL. VIII FEBRUARY, 1950 No. 2

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Contents continued on page 7

when MIGRAINE attacks

FIRST EFFECTIVE

oral TREATMENT

OF MIGRAINE ATTACK

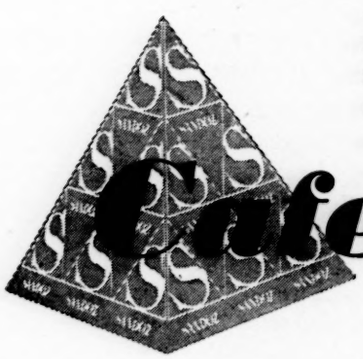
Sandoz proudly announces the *first effective oral* treatment of migraine—

Clinical investigation[1] demonstrated that 80% of a series of cases experienced good results. Best results were obtained in migraine, histamine and tension headaches.

Friedman,[2] in a large series of migraine cases, found Cafergone 55% more effective than ergotamine tartrate alone.

Later reports[3, 4] were equally favorable.

1. Horton, B.T., Ryan, R. E. & Reynolds, J. L., Proc. Staff Meet. Mayo Clinic, 23:105, Mar. 3, 1948.
2. Friedman, A. P., N. Y. State Jl. of Med. (in press).
3. Ryan, R. E., Postgraduate Medicine (in press).
4. Hansel, F. K., Annals of Allergy (in press).



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The American Journal of Medicine

VOL. VIII FEBRUARY, 1950 NO. 2

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Case Reports

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*Among the richest known sources of vitamin C are the citrus fruits. They also contain vitamins A, B_1 and P, and readily assimilable natural fruit sugars, together with other factors such as iron, calcium, citrates and citric acid.

References:

1. Gordon, E. S.: Nutritional and Vitamin Therapy in General Practice, Year Book Pub., 3rd ed., 1947.
2. Manchester, T. C.: Food Research, 7:394, 1944.
3. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944.
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5. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1948.

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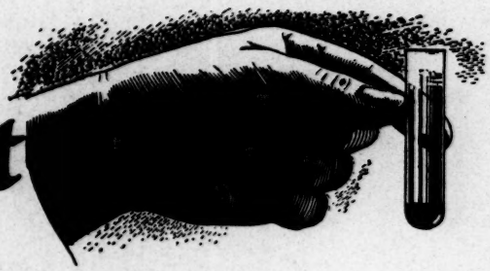

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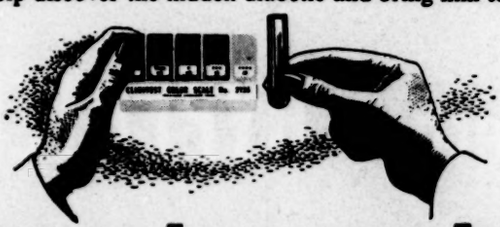
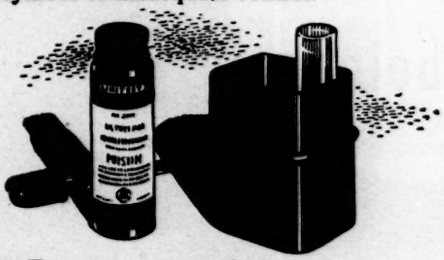
Early vigorous treatment of diabetes increases the patient's chances for longevity. One million diabetics remain undetected in the United States.* The diabetic must be detected before it is "*too late.*" ***Selftester***—for the general public, is a simple home test for the detection of urine-sugar. Its purpose is to help discover the hidden diabetic and bring him to the physician for adequate care.



Control must be complete

A well-controlled diabetic is less susceptible to infection and acidosis. The incidence of vascular complications, retinitis, gangrene, and renal intercapillary glomerulosclerosis is reduced with vigorous control. "*Too little*" is the symbol of inadequate control.



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*Joslin, E. P., Postgrad. Med.: 4:302 (Oct.) 1948.
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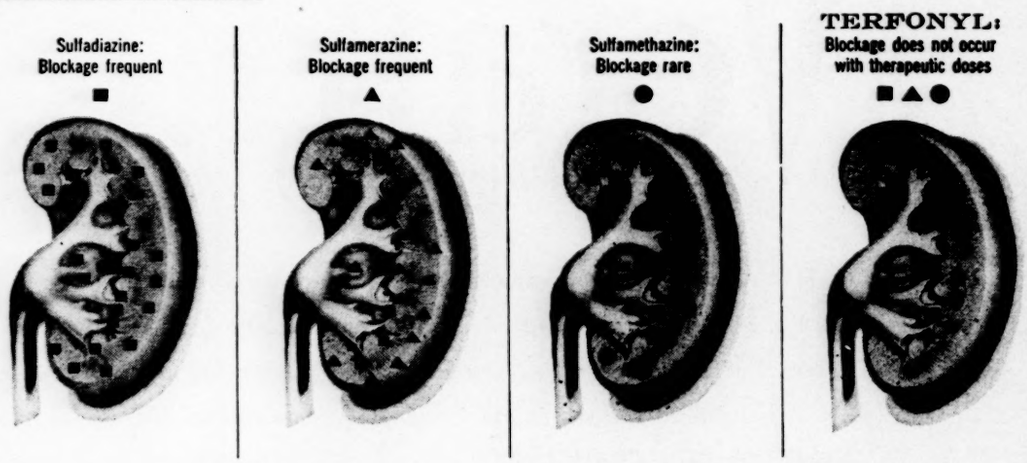

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bibliography: (1) Donovan, M. A.: New York State J. Med. *45*:1756, 1945. (2) Reaser, P. B., and Burch, C. E.: Proc. Soc. Exper. Biol. & Med. *63*:543, 1946. (3) Griggs, D. E., and Johns, V. J.: California Med. *69*:133, 1948. (4) Chapman, D. W., and Schaffer, C. F.: Arch. Int. Med. *79*:449, 1947. (5) Modell, W.; Gold, H., and Clarke, D. A.: J. Pharmacol. & Exper. Therap. *84*:284, 1945. (6) Finkelstein, M. B., and Smyth, C. J.: J. Michigan M. Soc. *45*:1618, 1946. (7) Gold, H., and others: Am. J. Med. *3*:665, 1947.

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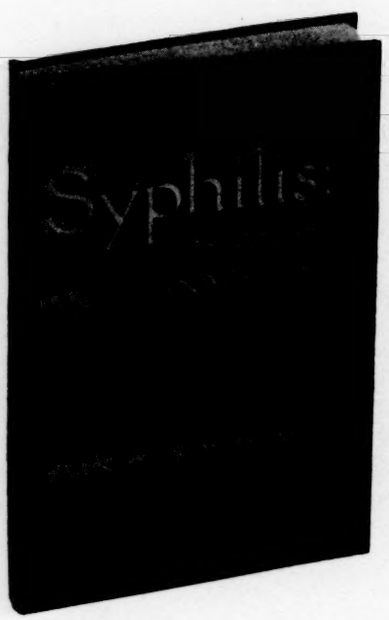

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by

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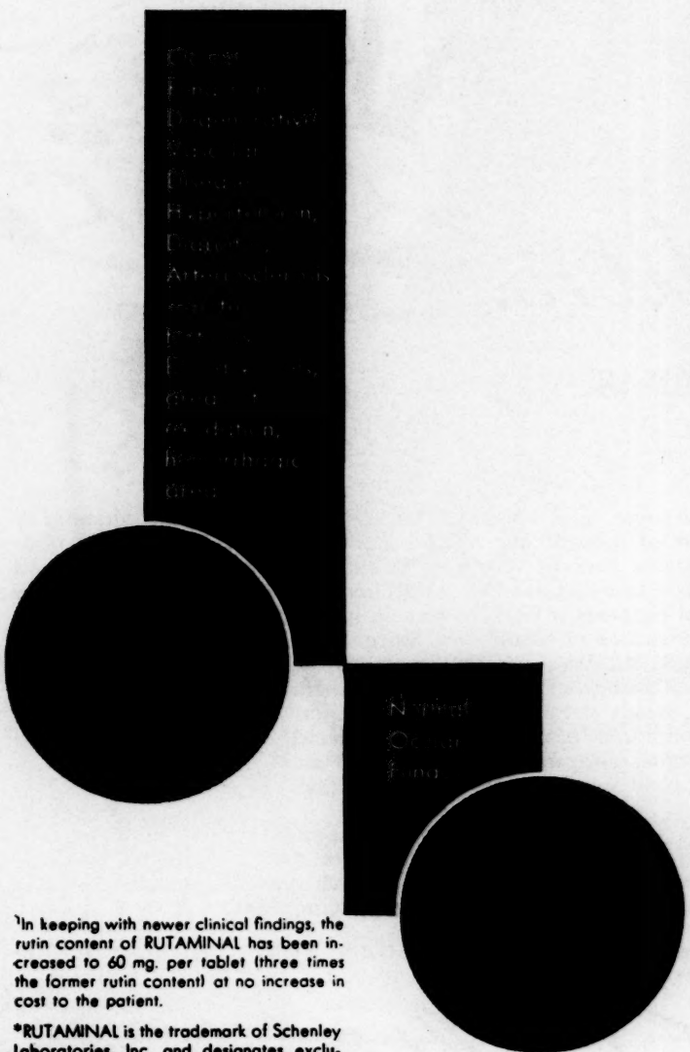

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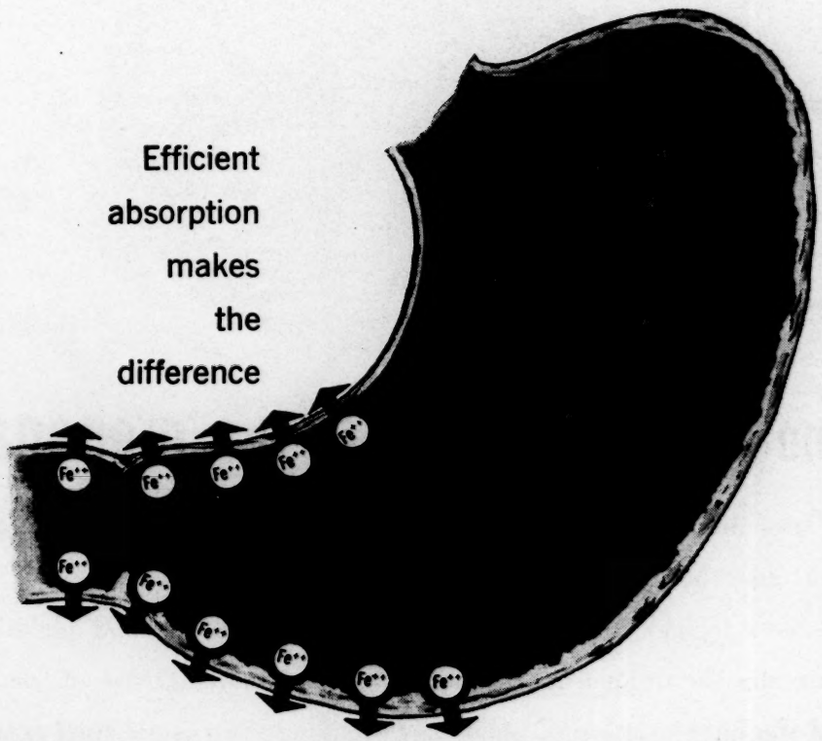
IRON	12 mg.	COPPER	0.5 mg.

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.



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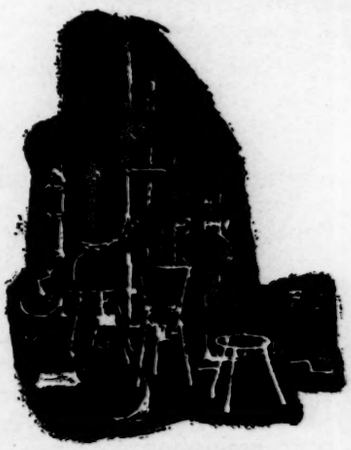
in resistant staphylococcal infections

Aureomycin



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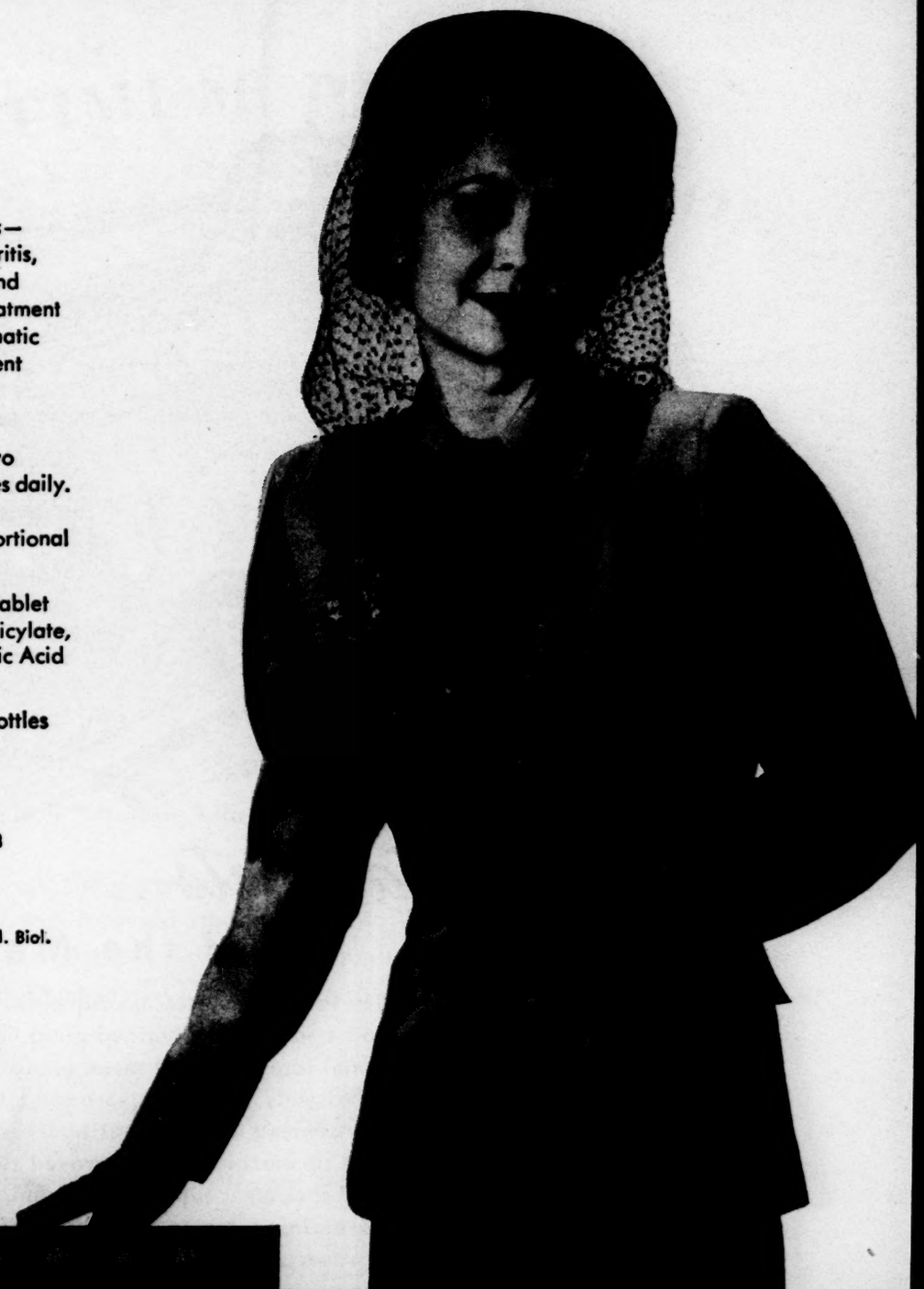

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SUPPLIED: Pabalate Tablets in bottles of 100 and 500. Liquid Pabalate in bottles of 1 pint.

REFERENCES:

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Para-aminobenzoic acid increases blood levels of concurrently administered salicylate.[2]

matic affections

Rx

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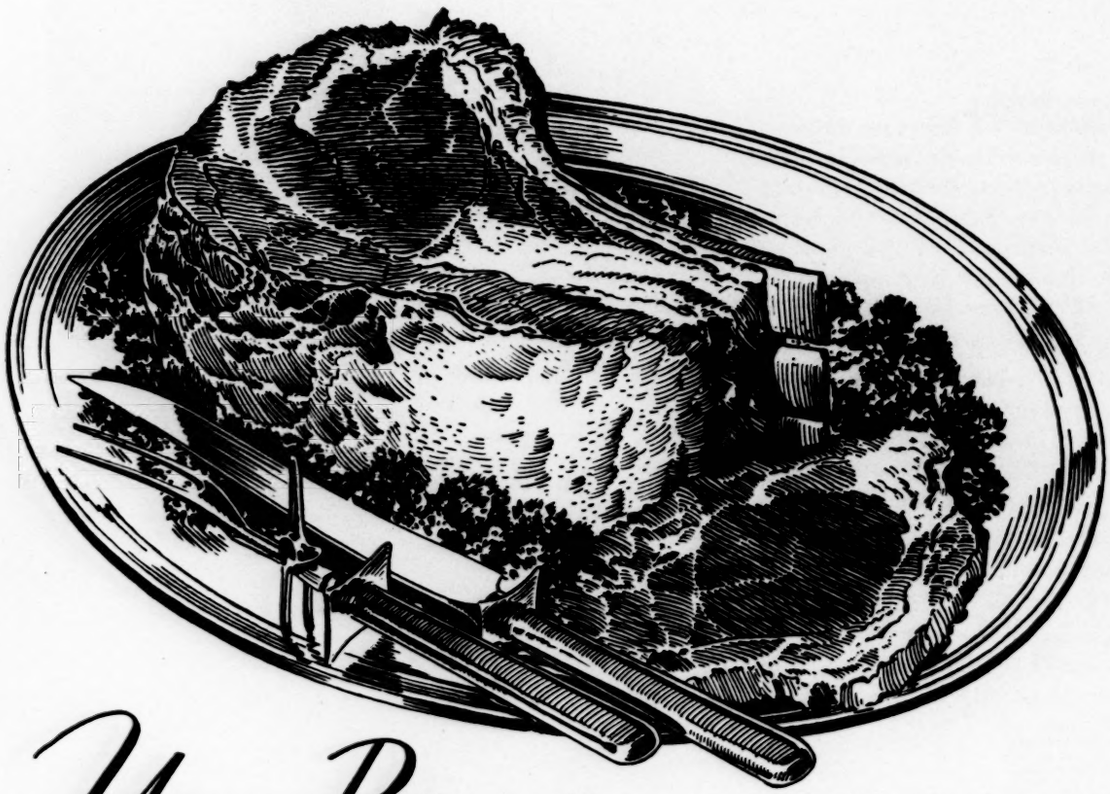

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*McLester, J. S.: Protein Comes Into Its Own, J.A.M.A. *139*:897 (April 2) 1949.

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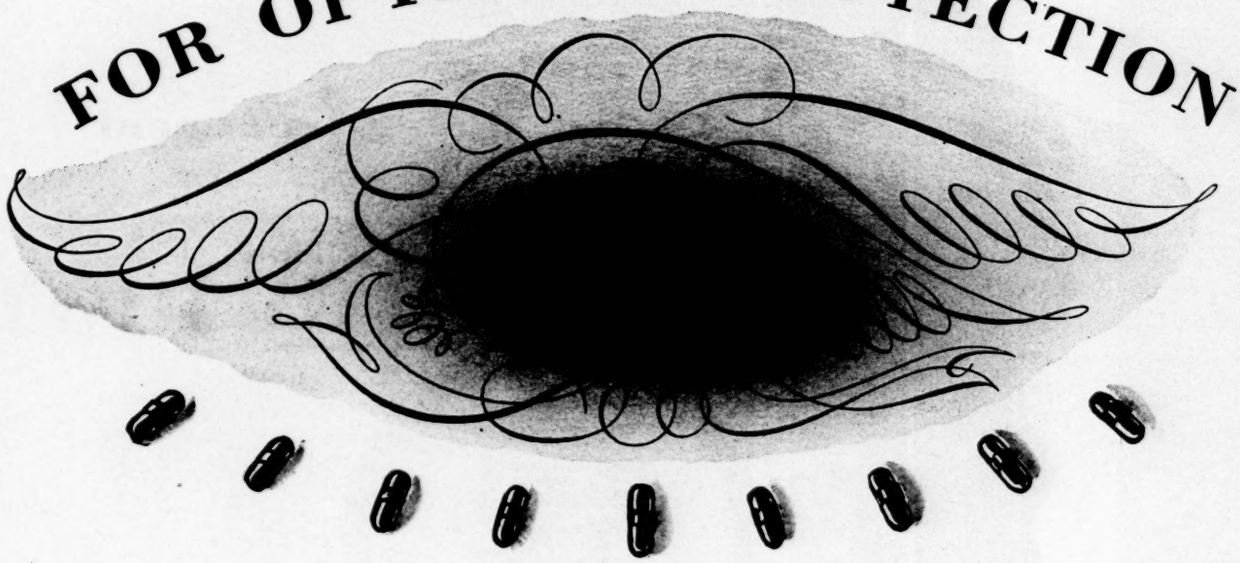

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(1) Henderson, E., and Seneca, H.: Am. J. Digest. Dis. *16*:372, 1949.
(2) Heineken, T. S., and Seneca, H.: Rev. Gastroenterol. *15*:611, 1948.

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Editorial

The Limits of Biomorphology

ANATOMY, one of the most ancient of the medical sciences, began in the dissecting room. Until the discovery of the microscope in the seventeenth century morphologists were limited to the study of those structures of the body which could be seen with the naked eye. Organography and organ pathology thus became the earliest disciplines of normal and morbid anatomy.

With the advent of microscopy a new era dawned. The visualization of structures less than one-thousandth the size of those discernible in the gross enabled anatomists and pathologists to study specific tissues and even individual cells of the human body. The resulting knowledge which accumulated in the fields of histology, cytology and microscopic pathology was either directly or indirectly responsible for many of the important advances in clinical medicine that have occurred since the days of van Leeuwenhoek.

The conventional limits of both normal and morbid histology are today highly artificial. They are determined by the resolving power of the oil immersion lens, or to be more precise, by the wave lengths of visible light. The recent discovery of the electron microscope has provided a means of extending appreciably the domain of microscopy, but biologic data based on the use of this new technic should be accepted with reservation. Since exposure to the electron beam is made *in vacuo*, only dried specimens can be studied. The beam itself may create artifacts by imparting negative charges upon structural elements and thus cause distortion through electrostatic forces. Important as the electron microscope is as a tool to biologists, it can at best only begin to penetrate the submicroscopic realm.

While morphologists have been endeavoring to increase their powers of visualization, biochemists have been exploring the submicroscopic through a very different approach. The science of chemistry deals with invisible reactions that are defined primarily by indirect means. The study of molecular structure has long been a subject of chemical research and in recent years much has been learned not only relating to the structural formulas of organic compounds contained in human tissues but also concerning the spatial arrangement of the individual atoms within these molecules. A relatively new branch of structural chemistry concerned with the constitution of high molecular polymers now appears to be drawing the chemist and cytologist closer together than ever before. Giant molecules composed of many polypeptides or polysaccharides united in long chains have been identified as integral constituents of protoplasm. The structure and physicochemical properties of these macromolecules, some of which are large enough to be visualized with the electron microscope, are of manifest importance to students of medicine.

That the gap between the cytologist and the structural chemist has not yet been bridged is clearly indicated by Frey-Wyssling's brilliant treatise, "Submicro-

scopic Morphology of Protoplasm and Its Derivatives."[1] Between the realms of macromolecular chemistry and cytology lies the morphology of "fine structure" or "micellar systems." High molecular polymers may arrange themselves in lattices of variable structure forming capillary pores of various sizes containing water and dissolved crystalloids. The side chains of the huge molecules determine the forces binding them together in micelles. Intermicellar forces in turn determine the structural viscosity of the protoplasmic gel. Similarly the "binding" of crystalloids and water within the gel reticulum depends upon the exposed side chains on the individual micelles. Some giant molecules form structures other than chains, existing as flakes or discs. Changes in molecular configuration may result in the transformation of gels to sols, a process apparently involved in the ameboid motion of living cells.[2]

Although "morphology is not an ultimate goal of science," it is obvious that the dynamic processes of cellular physiology cannot be understood without an intimate knowledge of protoplasmic structure. The ultimate goal of biomorphology is the comprehension of the spatial arrangement of organic matter. The units involved are atoms and molecules rather than elements visible to the microscopist. Medical morphologists can no longer concern themselves merely with structures that can be *seen*. Indirect methods, based upon the techniques of physics and chemistry, must be employed to divulge the intricate structural relations of the submicroscopic realm. Knowledge is already accumulating rapidly in this important area of medical science. As an understanding of the structure of protoplasm unfolds, anatomy, biochemistry and physiology will be drawn closer together, and the teaching of preclinical sciences to medical students will inevitably require reorientation. Pathologic anatomy will become a very different subject from what it is today. The benefits which will accrue to patients as a result of the physicians' knowledge of submicroscopic pathology are beyond prediction.

W. Barry Wood, M.D.

[1] Frey-Wyssling, A. Submicroscopic Morphology of Protoplasm and Its Derivatives. New York, 1948. Elsevier Publishing Co., Inc.

[2] DeBruyn, P. P. H. Theories of amoeboid movement. *Quart. Rev. Biol.*, 22: 1, 1947.

Clinical Studies

Cerebral Blood Flow in Vascular Disease of the Brain*

With Observations on the Effects of Stellate Ganglion Block

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CHRONIC cerebral vascular disease is one of the common causes of disability and death. Because of the difficulty of access to the brain in life and the difficulties inherent in neuropathologic technics the natural history of cerebral vascular disease has not been studied extensively. The nitrous oxide technic for measuring cerebral blood flow devised by Kety and Schmidt[1] permits the investigation of the blood flow to and the oxygen utilization of the brain in various stages of this disease. The purpose of this report is to record the findings in the use of this technic in twenty-nine observations on twenty-three patients with cerebral vascular disease. Observations were made on patients with and without changes in their mental status resulting from the disease. The effect of unilateral stellate ganglion block on the cerebral circulation was studied in nineteen subjects.

METHOD

All of the subjects with cerebrovascular disease in this study had hypertension except one (A. C., Table II), a young man who had suffered repeated cerebral emboli from mitral stenosis. Patients with uncomplicated hypertension are not included. All studies were made on either middle aged persons with hypertension and diabetes or on patients with a history of a cerebral vascular accident.

The patients were divided into two groups: (1) those with normal and (2) those with abnormal mental status. Several patients with cerebrovascular accidents were included in the group with normal mental status. Routine mental status examinations were done on each subject at the time of the study. Patients who were disoriented, stuporous or comatose were classified as abnormal. Questionable defects in mental status were disregarded unless agreed on by all observers. The patients with acute cerebral vascular thrombosis were studied on the side of the suspected cerebral lesion, that is, blood was obtained from the internal jugular bulb on that side. Seven bilateral flows were done, blood being obtained from both internal jugular bulbs simultaneously.

Stellate ganglion blocks were done in three types of patients: (1) normal young individuals; (2) patients with hypertensive vascular disease and (3) patients with acute cerebral thrombosis. The blocks were done by the observer, using 4 to 8 ml. of 2 per cent procaine hydrochloride. They were not considered successful unless a Horner's syndrome associated with an increase in temperature of the ipsilateral arm resulted. In those patients with a history of a cerebrovascular accident, either fresh or old, the block was done on the side of the suspected cerebral lesion. The cerebral blood flow was always measured on the same side that the block was done, and in four instances bilateral blood flow determinations were done on individuals on whom unilateral stellate blocks had been done.

The nitrous oxide procedure of cerebral blood flow has been described in detail by Kety and Schmidt.[1] The modification which is in use

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in this laboratory, of drawing continuous arterial and venous samples rather than five separate arterial and venous samples for the determination of the mean arteriovenous nitrous oxide difference, was described in a previous paper[2] together with values for normal subjects. arterial and venous samples in order to obtain a true mean arteriovenous oxygen difference during the same period that the blood flow was measured. Arterial and venous samples were drawn immediately before and after each cerebral blood flow for glucose determination

TABLE I

PATIENTS WITH HYPERTENSION AND CEREBRAL VASCULAR DISEASE WITH NORMAL MENTAL STATUS

Pt.	Age	Diagnosis and Symptoms	Cerebral Blood Flow (ml./ min./ 100 gm. brain)	A-V O_2 Diff. (vol. %)	A-V Glucose Diff. (mg. %)	Cerebral Oxygen Utilization (ml. O_2/ min./ 100 gm. brain)	Cerebral Glucose Utilization (mg. glucose/ min./100 gm. brain)	Mean Arterial Pressure (mm. Hg)	Cerebral Vascular Resistance (mm. Hg/ml. blood/ 100 gm. brain/ min.)
L. S.	53	HVD, diabetes mellitus, neuropathy	46	9.89	12	4.5	5.5	120	2.60
O. P.	55	HVD, diabetes mellitus	47	7.55	11	3.55	5.2	110	2.34
N. H.	69	HVD, arteriosclerosis	..	6.93	....	....	....	133	
C. I.	53	HVD, retinopathy grade IV	64	7.78	12	4 9	7.7	187	2.90
D. B.	50	HVD, cerebrovascular accident 5 days previously	53	8.5	17	4.5	9.0	99	1.86
E. H.	47	HVD, cerebrovascular accident 2 yr. 7 mo. previously	R 51 L 48	R 6.37 L 6.75	R 10 L 10	R 3.23 L 3.24	R 5.10 L 4.80	... 145	2.9 2.9
D. D.	28	HVD, papilledema, retinal arteriolar spasm, cerebrovascular accident 1 yr. before	72	5.43	7	3.91	5.0	158	2.2
J. S.	41	HVD, retinopathy, grade IV, cerebrovascular accident 2 weeks previously	59	6.87	15	4.05	8.84	148	2.51
T. McC.	48	HVD, cerebrovascular accident 1 week previously	48	8.75	14	4.20	6.72	125	2.60
G. W.	65	HVD, cerebrovascular accident 12 hours previously	51	8.55	8	4.36	4.1	110	2.2
Mean		.....	54	7.58	11.6	4.00	6.2	133	2.5

R = right; L = left.

The gas mixtures used in the determinations of cerebral blood flow consisted of 15 per cent N_2O, 64 per cent N_2 and 21 per cent O_2. Arterial pressures were measured every two minutes during the blood flow determinations by the auscultatory method with the arm at heart level. Mean pressures were calculated from these readings by adding one-third of the pulse pressure to the diastolic pressure. The attributes of this method of determining mean pressure have been discussed previously.[2] The blood oxygens were determined by the spectrophotometric method described by Hickam and Frayser.[3] This was done on the integrated which was done by Nelson's photometric adaptation of the Somogyi method.[4] The average of the two arteriovenous glucose differences for each flow is used as the result. Cerebral oxygen utilization, cerebral glucose utilization and cerebrovascular resistance were calculated in this manner: Cerebral oxygen utilization $(CMRO_2) = CBF \times \frac{A-V\ O_2}{100}$ in ml. O_2/ min./100 gm. brain. Cerebral glucose utilization $(CMR\ Gl.) = CBF \times \frac{A-V\ glucose}{100}$ in mg. glucose min./100 gm. brain. Cerebrovascular

resistance (CVR) = $\frac{\text{mean arterial pressure}}{\text{CBF}}$ in mm. Hg/ml. blood/100 gm. brain/min.

RESULTS

Cerebral Vascular Disease. The results are summarized in Tables I, II and III. In this study significant differences indicate a p value of less than 0.01. The subjects with normal mental status (Group I) will be considered first: The cerebral blood flows in this group ranged from 46 to 72 ml./min./100 gm. brain, with a mean of 54. This differs significantly from the mean of 65 obtained in this laboratory in normal subjects. The normal values from this laboratory are higher than those reported by Kety et al.[1] The arteriovenous oxygen differences ranged from 5.43 to 9.89 volumes per cent, with a mean of 7.58. This differs significantly from the mean of 6.1 obtained in normals. The mean cerebral oxygen utilization, cerebral arteriovenous glucose difference, cerebral glucose utilization and

TABLE II

PATIENTS WITH HYPERTENSION AND CEREBRAL VASCULAR DISEASE WITH ABNORMAL MENTAL STATUS

Pt.	Age	Diagnosis and Symptoms	Cerebral Blood Flow (ml./min./100 gm. brain)	A-V O_2 Diff. (vol. %)	A-V Glucose Diff. (mg. %)	Cerebral Oxygen Utilization (ml. O_2/min./100 gm. brain)	Cerebral Glucose Utilization (mg. glucose min./100 gm. brain)	Mean Arterial Pressure (mm. Hg)	Cerebral Vascular Resistance (mm. Hg/ml. blood 100 gm. brain/min.)
W. P.	65	HCVD, acute cerebrovascular accident with aphasia and confusion	36	9.53	12	3.42	4.32	120	3.35
C. P.	35	Subarachnoid hemorrhage, conscious but confused	R 40 L 35	R 6.3 L 7.1	.. ..	R 2.52 L 2.48	....	88	2.3
A. C.	37	Mitral stenosis, repeated cerebral emboli, disoriented	R 32 L 35	R 7.7 L 7.7	R 8 L 8	R 2.46 L 2.68	R 2.56 L 2.80	97	2.94
N. W.	45	HVD, encephalomalacia	33 36 33	7.98 7.90 7.76	12 12 12	2.64 2.84 2.56	3.96 4.31 3.96	129 130 129	3.91 3.58 3.91
C. C.	50	HVD, encephalopathy, retinopathy grade IV	38	7.45	11	2.8	4.2	143	3.76
H. C.	57	HVD, encephalopathy, confusion	41 42	6.75 6.67	6 6	2.8 2.8	2.5 2.5	180 180	4.3 4.3
J. B.	62	HVD, encephalomalacia, confused and aphasic	39	7.57	12	2.95	4.7	118	3.03
O. W.	63	HVD, episodes of poor orientation, memory defects, well oriented	R 44 L 43	R 5.24 L 5.72	R 5 ..	R 2.31 L 2.57	R 2.20	110	2.50
H. S.	55	HVD, emotional lability and personality changes following cerebral vascular accident	48	5.92	11	2.90	5.3	107	2.2
C. P.	49	HVD, 3 strokes, aphasia, personality changes by history	39	8.65	17	3.37	6.8	155	3.97
J. O.	62	HVD, acute stroke, aphasic and confused	58	6.17	12	3.60	7.0	177	3.05
A. P.	57	HVD, acute stroke, branch left middle cerebral artery, unconscious	.. ..	R 5.4 L 5.3	R 10 L 12	....	....	110	
J. D.	57	HVD, encephalopathy, confused	48	8.13	14	3.90	6.70	117	2.56
Mean		.....	**40**	**7.10**	**10.6**	**2.87**	**4.4**	**131**	**3.3**

R = right; L = left.

$\frac{\text{A} - \text{V glucose}}{\text{A} - \text{V oxygen}}$ ratio were all within normal limits. The mean arterial pressures ranged from 99 to 187 mm. Hg, with a mean of 133 mm. Hg, as compared to a mean of 83 mm. Hg in the normal subjects. The cerebrovascular resistance varied from 1.86 to 2.9, with a mean of 2.5 mm. Hg/ml. blood/100 gm. brain/min. This differs significantly from the mean of 1.3 obtained in normals.

Those subjects with abnormal mental status (Group II) showed the following results: Cerebral blood flows ranged from 32 to 58, with a mean of 40. This represents a significant variation not only from the normal but also from Group I. The mean arteriovenous oxygen difference did not differ significantly from that in Group I but did differ from the normal. The arteriovenous glucose difference fell within the normal range. The cerebral oxygen utilizations varied from 2.3 to 3.9, with a mean of 2.87. This is a significant difference from the normal (3.8) and from Group I. The cerebral glucose utilization ranged from 2.2 to 7.0, with a mean of 4.4. This represents a significant difference from the normal (6.2) and Group I. The $\frac{\text{A} - \text{V glucose}}{\text{A} - \text{VO}_2}$ ratios are within normal limits. The mean arterial pressures ranged from 88 to 180, with a mean of 131, almost identical with that of Group I. The cerebrovascular resistance ranged from 2.2 to 4.3, with a mean of 3.3. This is a significant variation from Group I as well as the normals. The great increase in cerebrovascular resistance over Group I, with identical average mean pressures in the two groups, would indicate that we are dealing with the effects of cerebral vascular disease rather than of hypertension alone.

TABLE III

COMPARISON OF CEREBRAL METABOLIC FUNCTIONS BETWEEN NORMALS AND SUBJECTS WITH CEREBRAL VASCULAR DISEASE, WITH AND WITHOUT CHANGES IN MENTAL STATUS

	Normals (33 Determinations)		Cerebral Vascular Disease with Normal Mental Status (11 Determinations)		Cerebral Vascular Disease with Abnormal Mental Status (18 Determinations)	
	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
Cerebral blood flow (ml./min./100 gm. brain)	65	2.1	54*	2.7	40†	1.6
A-V O_2 difference (vol. %)	6.1	0.14	7.58*	0.39	7.10*	0.3
A-V glucose difference (mg. %)	9.9	0.42	11.6	0.9	10.6	0.78
Cerebral O_2 utilization (ml.O_2/min./100 gm. brain)	3.79	0.09	4.00	0.17	2.87†	0.1
Cerebral glucose utilization (mg. glucose/min./100 gm. brain)	6.2	0.26	6.2	0.56	4.40†	0.43
Arterial pressure (mm. Hg)	83	....	133*	....	131*	
Cerebrovascular resistance (mm. Hg/ml. blood/100 gm. brain/min.)	1.3	0.04	2.5*	0.11	3.3†	0.18
$\frac{\text{A-V glucose}}{\text{A-V } O_2}$ ratio	1.67	0.06	1.53	0.09	1.53	0.1

* Significant variation from normal.

† Significant variation from normal and from group with normal mental status.

Significant P values < 0.01

$$\text{Std. Error} = \sqrt{\frac{\epsilon x^2 - \frac{(\epsilon x)^2}{n}}{n-1}} \Big/ \sqrt{n}$$

TABLE IV

EFFECT OF STELLATE GANGLION BLOCK ON CEREBRAL METABOLISM FUNCTIONS

Pt.	Age	Diagnosis and Symptoms	Side Blocked	Cerebral Blood Flow (ml./min./100 gm. brain)		A-V O_2 Diff. (vol. %)		A-V Glucose Diff. (mg. %)		Cerebral Oxygen Utilization (ml. O_2/min./100 gm. brain)		Cerebral Glucose Utilization (mg. glucose/min./100 gm. brain)		Mean Arterial Pressure (mm. Hg)		Cerebral Vascular Resistance (mm. Hg/ml. blood/100 gm. brain/min.)	
				Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
J. A.	62	Thrombosis, branch left middle cerebral artery 5 hours before	Left	58	50	6.17	6.61	12	12	3.6	3.3	6.96	6.02	177	175	3.05	3.54
D. B.	50	Left hemiparesis, recurrent	Right	53	49	8.51	7.80	17	15	4.5	3.82	9.00	7.36	99	100	1.86	2.02
A. P.	57	Embolism, branch left middle cerebral artery 2 hours before	Left	..	...	R 5.4	R 5.9	R 10	R 11								
				..	...	L 5.3	L 5.2	L 12	L 11	....	....	....	....	110	110		
				R 75	R 60	R 6.5	R 6.3	R 13	R 11	R 4.9	R 3.8	R 9.7	R 6.6	...	...	R 1.27	R 1.59
W. M.	30	Normal	Left	L 70	L 53	L 6.6	L 6.3	L 14	L 12	L 4.8	L 3.4	L 9.7	L 6.4	95	96	L 1.36	L 1.79
E. H.	47	Left hemiparesis 7 months ago, HVD	Right	R 51	R 48	R 6.4	R 6.8	...	R 10.	R 3.2	R 3.2	....	R 4.8				
				L 50	L 47	L 6.5	L 7.1	...	L 13	L 3.2	L 3.3	....	L 6.1	145	147	2.9	3.13
G. W.	65	Thrombosis, branch left middle cerebral artery 12 hr. before	Left	51	47	8.6	8.9	8	8	4.4	4.2	4.1	3.8	110	110	2.16	2.35
C. J.	53	HCVD, retinopathy grade IV	Right	66	80	7.2	6.8	14	10	4.7	5.4	9.2	8.1	187	187	2.83	2.31
J. B.	62	Right hemiparesis for 6 weeks, HVD	Left	39	31	7.6	6.9	11	13	2.95	2.13	4.7	3.1	118	119	3.03	3.84
O. W.	63	HVD	Right	R 44	R 37	R 5.2	R 6.7	R 5	R 9	R 2.3	R 2.5	R 2.2	R 3.3	...	...	....	R 2.8
				L 45	L 32	L 5.7	L 6.9	...	L 7	L 2.6	L 2.2	....	L 2.2	110	103	2.5	L 3.2
J. C.	63	HCVD, retinopathy grade IV	Left	60	64	3.5	3.8	5	3	2.1	2.4	3.0	1.9	139	121	2.32	1.89
C. C.	50	HCVD, encephalopathy	Right	54	55	5.9	6.2	8	8	3.2	3.4	4.3	4.4	169	169	3.13	3.08
J. D.	57	Encephalomalacia	Right	48	36	8.13	8.10	14	15	3.9	2.9	6.7	5.5	117	96	2.56	2.61
W. M.	22	Normal	Right	53	55	5.2	5.5	9	9	2.7	3.0	4.77	4.95	73	80	1.38	1.45
D. D.	28	HVD, retinopathy grade III	Left	72	71	5.4	5.4	7	..	3.9	3.9	5.0	....	158	150	2.2	2.1
J. H.	18	Normal	Right	70	72	5.62	5.47	7	8.	3.93	3.93	4.9	5.8	89	89	1.27	1.24
J. McL.	30	Normal	Left	64	48	5.7	6.3	7	11	3.6	3.0	4.5	5.3	89	83	1.39	1.72
V. R.	33	Normal	Right	58	58	5.8	5.9	...	...	3.4	3.4	....	....	83	82	1.43	1.42
L. J.	21	Normal	Right	..	...	6.1	5.7	8	8	...	...	....	....	70	75		
L. H.	34	HVD, retinopathy grade IV	Right	..	...	5.5	5.5	9	8	...	...	....	....	130	125		
Mean			.....	57	54	6.22	6.29	9.9	9.6	3.6	3.4	5.7	5.2	122	119	2.2	2.3
Standard Error			.....	2.2	3.3	0.3	0.25	0.8	0.8	0.16	0.12	0.40	0.38	...	...	0.1	0.09

R = right; L = left.

Stellate Ganglion Block. The results are summarized in Table IV. In none of the three types of patients studied, namely, normal young persons, patients with hypertensive vascular disease and patients with acute cerebral thrombosis, did unilateral stellate ganglion block produce a significant change in any of the cerebral metabolic functions.

Of the nineteen subjects studied six had no evidence of vascular disease and were all under thirty-five years of age. Two young subjects (D. O. and L. H., Table IV) had hypertension with associated severe retinal arteriolar spasm. There was no change in the appearance of these vessels following stellate block. Bilateral determinations of cerebral blood flow and oxygen utilization were made on three patients and bilateral arteriovenous oxygen and glucose differences determined in a fourth before and after unilateral stellate block. There was no significant difference in the values for the two sides either before or after the block.

COMMENTS

Since the nitrous oxide method measures the cerebral blood flow per minute per unit weight of brain, theoretically normal values would be obtained if a considerable portion of brain tissue were removed or rendered functionless as long as the remaining part of the brain retained normal cellular function. A simple reduction in blood flow per 100 gm. of brain, without alteration in cerebral metabolism, is shown by a fall in blood flow and a rise in arteriovenous oxygen and glucose differences. Disease specifically affecting brain cells and not involving cerebral vessels, such as insulin coma, should show a normal blood flow and a fall in cerebral arteriovenous oxygen and glucose differences. When cerebral metabolism has become impaired because of an original reduction in cerebral blood flow, measurements should indicate a decreased cerebral blood flow and a normal or only slightly increased arteriovenous oxygen and glucose difference.

Any division of hypertensive patients into those with no cerebral vascular disease and those with cerebrovascular disease without overt symptoms is necessarily arbitrary. Such patients, for example, have as much generalized cerebral vascular disease the day prior to a small cerebral vascular accident as the day following; the death of a small area of brain may cause marked symptoms and neurologic findings but have little effect on total blood flow. The results of these studies indicate that there must be several stages in the progression of the natural history of vascular disease of the brain. The subjects in Group I, namely, those with hypertension and diabetes and those with cerebrovascular accidents and normal mental status, would seem to represent a relatively early stage. They showed a moderate reduction in cerebral blood flow and an increased arteriovenous oxygen difference, with a resulting normal cerebral oxygen utilization. It is logical to assume that the reduction in blood flow is the result of diffuse vascular disease and not hypertension *per se*, since Kety and colleagues[5] have shown that in uncomplicated hypertension the cerebral blood flow and arteriovenous oxygen difference are normal although the cerebrovascular resistance is increased. The reduction in blood flow does not appear to be related to the age of the patients, for other observations here and in Kety's laboratory[5] indicate no correlation between age and cerebral blood flow or between age and cerebral oxygen or glucose metabolism.

The cerebral vascular disease in the subjects in Group I might be local or diffuse. If disease has progressed sufficiently in one area of the brain to result in local tissue necrosis, the blood flow, as we measure it, might not be affected for the necrotic area might be excluded completely from the circulation. Thus a history of a cerebrovascular accident, with resulting neurologic signs, may be perfectly consistent with normal values for cerebral metabolism as measured by this method.

The subjects in Group II, those with alterations in mental status as a result of vascular disease of the brain, represent a later stage in the progression of the disease. The blood flow shows a considerable decrease (38 per cent) over the normal while the arteriovenous oxygen and glucose differences are only slightly increased and normal, respectively. This results in a fall in cerebral oxygen and glucose consumption, which correlates well with the alterations in mental status that these patients manifested. A similar decrease in blood flow to the kidney has been noted in subjects with advanced hypertensive vascular disease.[6]

The decrease in cerebral metabolism is related to the inability of the brain cells to extract more oxygen and glucose per unit of blood rather than to the low blood flow itself. In the presence of normal cell function a reduction of blood flow of at least 21 per cent may be completely compensated for by a widening of the A-V oxygen difference. Subjects who stand motionless[2] maintain normal cerebral metabolism in this way. In heart failure a reduction in blood flow of 40 per cent is not completely compensated by widening of the A-V oxygen difference, but decrease in oxygen consumption is much less than in the subjects reported herein.[7] The finding in patients in Group II of a low blood flow without a sufficient increase in A-V oxygen difference to give normal values for cerebral metabolism is interpreted as evidence of abnormally functioning brain tissue. This poor cellular function results in some way from the progressive vascular disease. Several possibilities exist: (1) Sufficient areas of softening and scarring may have occurred so that part of the blood supply to the brain passes through areas of scar tissue. (2) Marked disturbances in function of uninjured cells may have resulted from the great disorder in total brain function produced by many local lesions. (3) In certain areas metabolism of existing cells may be greatly deranged by reductions in cerebral blood flow to a level incompatible with normal function but not sufficient to cause death. (4) Infection and altered metabolism in other organs may secondarily affect brain metabolism. Further experimental work is needed to explore these possibilities.

While these data do not explain the vulnerability of the cerebral vessels of patients with hypertension to thrombosis and hemorrhage, they do show, in a quantitative manner, that cerebral metabolism is altered in many such patients and that this metabolic defect is probably related to the greatly increased resistance offered to the flow of blood by the diseased cerebral vessels. The failure of the cerebral blood flow to increase in these patients following stellate ganglion block would indicate that the increased cerebrovascular resistance is not due to increased tone mediated by the sympathetic nervous system.

The importance of local vasomotor control in the regulation of the cerebral circulation has long been debated. The observations on monkeys by Penfield[8] indicating that complete removal of all the sympathetic nerve fibers which enter the cranial cavity on the carotid and vertebral arteries does not appreciably reduce the number of normal intracranial perivascular nerve fibers lend support to the idea that the sympathetics do not greatly influence cerebral vascular tone. Other data[9,10] gathered by direct observation of the pial vessels of cats confirm this notion. An additional piece of indirect evidence of the lack of direct sympathetic influence on the cerebral circulation are observations which indicate the apparent constancy of the cerebral blood flow in the same individual[2,11] as opposed to the great variability of blood flow in a part known to be under sympathetic influence, such as the skin. Since stellate ganglion block is thought to interrupt the sympathetic pathways to the head on the ipsilateral side, the present observations tend to confirm those made by less quantitative means. As a matter of fact our data would indicate that in a larger series of observations one might expect to find a

decrease in cerebral blood flow after stellate block. A possible explanation of this is that more blood might be directed to the skin and subcutaneous tissue of the face after the block. In view of this it is difficult to explain the apparent successes reported in the treatment of apoplexy by stellate block.[12,13,14] Certainly all clinical observations following a therapeutic procedure must be tempered by the knowledge that spontaneous changes frequently occur. A final opinion on the value of stellate block cannot be given until observations are made on the effect of block in persons with ligation of one internal carotid artery or on young individuals with recent cerebral embolism. It is possible that in young persons, without evidence of vascular disease, an abnormal state of cerebral vascular tone could be produced by such a stimulus. This situation was produced experimentally by Villaret and Cachera in animals.[15] This increase in tone could possibly be abolished by sympathetic block; however, we have not had the opportunity to make these observations.

SUMMARY

1. Values for cerebral blood flow per 100 gm. of brain, arteriovenous oxygen difference, arterio-venous glucose difference, cerebral oxygen utilization, cerebral glucose utilization and cerebrovascular resistance are given in twenty-nine observations on twenty-three patients with cerebral vascular disease. The subjects were either middle aged persons with hypertension and diabetes or patients with a history of a cerebral vascular accident. They were divided into those with normal and those with abnormal mental status.

2. Those patients who had no alteration in their mental status had significantly lower cerebral blood flows, higher arteriovenous oxygen differences and higher cerebrovascular resistances than normal young persons. Cerebral oxygen and cerebral glucose utilizations were normal.

3. The subjects with abnormal mental status resulting from cerebral vascular disease had significantly lower cerebral blood flows, cerebral oxygen and glucose utilizations and higher cerebrovascular resistances than those with normal mental status or than normal young subjects.

4. It is believed that these groups represent two stages in the natural progression of cerebral vascular disease.

5. Unilateral stellate ganglion block produced no change in cerebral metabolic functions in normals, patients with hypertensive vascular disease and elderly patients with cerebral thrombosis. The significance of this is discussed.

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Cerebral Circulation in Heart Failure*

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CLINICAL evidences of disturbed cerebral function are not uncommon in heart failure. Such patients may present signs of irritability, apathy, extreme drowsiness and, occasionally, disorientation. Heretofore the mechanisms whereby these disturbances occur, and the possible influences of alterations in the cerebral metabolism on other bodily functions in heart failure, have not been investigated quantitatively because of lack of methods for measuring cerebral blood flow. The present report deals with data which have been collected in sixteen observations on fourteen subjects with heart failure, using the nitrous oxide technic for cerebral blood flow, as devised by Kety and Schmidt.[1] The patients studied were considered clinically to have chronic congestive heart failure with low cardiac output; that is, all required sodium restriction and mercurial diuretics to prevent dyspnea and edema while at rest. They had no complicating illnesses which would have been expected to cause an increase in cardiac output. Patients with anemia (hemoglobin less than 11 gm.) are not included in this study.

METHODS

All the subjects were studied under fasting conditions. If the patient were orthopneic, the table was tilted so that his head was elevated about 10 degrees. No patient was thought to be in an abnormal mental state at the time of the study. The nitrous oxide procedure for measuring the cerebral blood flow has been described in detail by Kety and Schmidt.[1] In this laboratory continuous ten-minute blood samples are drawn simultaneously from the femoral artery and the internal jugular vein for the determination of the mean arteriovenous nitrous oxide difference. This modification of the method and data on values for normal young subjects has been reported previously.[2] The gas mixture used in the determination consisted of 15 per cent N_2O, 64 per cent N_2 and 21 per cent O_2. Arterial pressures were measured by the auscultatory method with the arm held at heart level every two minutes during the blood flow determination. Mean pressures were calculated from these readings by adding one-third of the pulse pressure to the diastolic pressure. Blood oxygen contents were determined by the spectrophotometric method of Hickam and Frayser.[3] Arterial and internal jugular venous blood samples for glucose determination were drawn immediately before and after each cerebral blood flow. Glucose was determined by Nelson's photometric adaptation of the Somogyi method.[4] The average of the two arteriovenous glucose differences for each flow is used as the result. Cerebral oxygen utilization, cerebral glucose utilization and cerebrovascular resistance were calculated as previously described.[1,2]

RESULTS

The results are summarized in Table 1. The mean values are the important figures because the variation from person to person and the technical errors involved in the procedure are too great to allow conclusions to be drawn from one set of observations or any particular patient. The mean cerebral blood flow was 40 ml./min./100 gm. brain, a 39 per cent reduction from the mean of 65 ml. obtained in this laboratory on normal young men. The mean cerebral arteriovenous oxygen difference was 8.6 volumes per cent, a 41 per cent increase over the normal mean of 6.1. The mean cerebral venous oxygen tension was 25 mm. Hg; the

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mean venous oxygen tension calculated for normal persons was 34 mm. Hg. In this calculation the average normal cerebral arteriovenous oxygen difference was 6.1 volumes per cent.

not strictly comparable. The normals were healthy young males thirty years of age or younger; eight of the cardiac patients were above forty years of age. Although preliminary observations here and in Kety's

TABLE I

CEREBRAL METABOLIC FUNCTIONS IN HEART FAILURE

Pt	Age	Sex	Diagnosis	Surface Area (sq. m.)	Cerebral Blood Flow (ml./ min./ 100 gm. brain)	Arterial-Cerebral Venous O_2 Difference (vol. %)	Cerebral Venous O_2 Tension (mm. Hg)	Arterial-Cerebral Venous Glucose Difference (mg. %)	Cerebral O_2 Utilization (ml. O_2/ min./100 gm. brain)	Cerebral Glucose Utilization (mg. glucose/ min./100 gm. brain)	Mean Arterial Pressure (mm. Hg)	Cerebral Vascular Resistance (mm. Hg/ ml. blood/ 100 gm. brain/ min.)	$\frac{\text{A-V Glucose}}{\text{A-V } O_2}$
J. M.	36	M	SHD—AI	1.82	38	7.31	....	19	2.77	7.2	110	2.96	2.60
W. G.	53	M	RHD—AI	1.67	46	8.03	....	.....	3.69	.....	83	1.81	
					44	8.79	....	.....	3.86	.....	79	1.80	
L. C.	31	F	RHD—MS, MI, AI	1.62	37	10.10	....	15	3.77	5.6	80	2.16	1.49
M. M.	36	F	HCVD	1.55	41	8.15	....	11	3.34	4.5	136	3.31	1.35
E. R.	57	M	Undetermined	1.70	29	10.76	18	13	3.12	3.8	100	3.45	1.21
					28	11.10	....	13	3.11	3.8	102	3.64	1.17
R. D.	47	M	Coronary disease	1.64	54	6.95	34	13	3.75	7.0	86	1.59	1.87
U. W.	61	M	Coronary disease	1.75	40	7.74	28	7	3.10	2.8	97	2.42	0.91
W. W.	28	M	RHD—MS, AI	1.61	41	9.28	22	15	3.80	6.2	100	2.44	1.62
M. S.	23	F	RHD—MS	1.56	49	5.15	33	11	2.53	5.1	87	1.77	2.04
A. J.	41	F	RHD—MS AF	1.47	29	10.87	18	18	3.16	5.2	69	2.38	1.66
N. C.	46	M	Coronary disease	1.80	28	10.76	20	15	3.01	4.2	100	3.60	1.39
J. B.	33	M	Undetermined	1.64	45	6.48	30	11	2.92	5.0	122	2.70	1.70
H. L.	39	M	HCVD	2.19	42	7.26	19	16	3.05	6.7	125	2.98	2.20
R. Q.	35	F	RHD—MS	1.49	44	8.20	30	11	3.61	4.9	102	2.32	1.34
			Cardiac patients:										
			Mean		40*	8.56*	25*	13.6*	3.29*	5.14*	99*	2.58*	1.61
			St. Dev.†		7.8	1.78	6	3.1	0.4	1.3	...	0.69	0.42
			S.E.‡		1.9	0.45	1.8	0.83	0.1	0.35	...	0.17	0.11
			Controls:										
			Mean		65	6.1	34	9.9	3.79	6.2	83	1.3	1.67
			St. Dev.†		12	0.81	....	2.39	0.55	1.4	...	0.24	0.35
			S.E.‡		2.1	0.14	....	0.42	0.09	0.26	...	0.04	0.06

* Indicates significant change from normal. All p values <0.01 except cerebral glucose utilization, which is <0.02.

† Standard Deviation = $S = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}{n-1}}$

‡ Standard Error = $\frac{S}{\sqrt{n}}$

SHD Syphilitic heart disease
HCVD Hypertensive cardio-vascular disease
MS Mitral stenosis
AF Auricular fibrillation
RHD Rheumatic heart disease
AI Aortic insufficiency
MI Mitral insufficiency

The mean arteriovenous glucose difference and mean cerebral vascular resistance in the patients with congestive failure were significantly increased over the normal. The mean cerebral oxygen consumption of 3.3 ml. O_2/min./100 gm. brain represents a significant decrease from the normal value of 3.8. The $\frac{\text{A-V glucose}}{\text{A-V } O_2}$ ratio remained normal.

The age groups of our normal subjects and of the patients in congestive failure are

laboratory[5] indicate no correlation between age and cerebral blood flow or other cerebral metabolic functions, a true statistical evaluation of this point has not yet been made.

Since cerebral blood flow by the nitrous oxide method is measured in ml. per unit weight of brain and since available data[6] show a poor correlation between brain weight and body size, no attempt has been made to convert our figures to standard surface area measurements.

COMMENTS

The nitrous oxide method would appear to be satisfactory for use in patients with congestive heart failure. It is possible that contamination of internal jugular blood by blood from extracranial sources may occur to a greater extent when the rate of flow in the internal jugular vein is slowed. Theoretically, this could result in a measured cerebral blood flow which was lower than the true value and a smaller arteriovenous oxygen difference than might have been found if uncontaminated internal jugular blood were measured. Unfortunately a sufficiently large series of observations on the effects of extracerebral contamination have not been made in order to decide this point definitely. Such studies are now in progress and will be reported later. Studies on normal subjects standing motionless show that under certain conditions a widened A-V oxygen difference will completely compensate for a large reduction in cerebral blood flow.[2] This would suggest that in this particular instance of slowed internal jugular flow extracerebral contamination had not occurred.

TABLE II
PERCENTAGE ALTERATIONS IN CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION AS COMPARED TO CARDIAC OUTPUT AND TOTAL O_2 CONSUMPTION IN HEART FAILURE

	Normals	Cardiacs	Change %
Cardiac index* (l./min./sq. m.)	3.54	2.10	−41
Total O_2 consumption* (ml./min./sq. m.)	134	146	+ 9
Cerebral blood flow (ml./min./100 gm. brain)	65	40	−39
Cerebral O_2 consumption (ml. O_2/min./100 gm. brain)	3.79	3.29	−13

*Data obtained from Stead et al.[7] See text for explanation.

The cerebral blood flow is reduced in chronic heart failure and the peripheral resistance is increased. While the cardiac output was not measured in these subjects, it seems fair to assume that the mean cardiac index was similar to that found in the series of patients with chronic failure reported by Stead et al.[7] and Myers.[8] The clinical criteria for selection of patients were similar in all three groups, and the average cardiac index in the two series in which the measurements were made was 2.1 and 2.2, respectively. The average reduction in cerebral blood flow in chronic failure is 39 per cent and the average reduction in cardiac output is 41 per cent. (Table II.) The reduction in blood flow to the brain is proportionate to the fall in cardiac output. In this respect the liver and brain behave similarly. By contrast, the reduction in blood flow to the kidney is out of proportion to the decrease in cardiac output.[9]

The rise in peripheral resistance in the cerebral vessels suggests that the reduction in blood flow is partially caused by vasoconstriction. The role of an increased venous pressure in the slowing of the cerebral blood flow was not investigated; but the increase in cerebral vascular resistance cannot be attributed to a rise in venous pressure unless the rise is considerably greater than that usually seen in chronic failure. The rise in total peripheral resistance in chronic heart failure and the increase in local resistance in the splanchnic area and the kidney have been shown to be unrelated.[7,8,9] There was no reason to suspect an increase in intracranial pressure, other than that related to changes in venous pressure, as a possible cause for the increased cerebral vascular resistance. These studies are compatible with the assumption that the increase in resistance in the cerebral vessels results from vasoconstriction. They do not elucidate the mechanism of the postulated vasoconstriction.

The brain differs from the splanchnic area in that it does not maintain normal oxygen consumption in heart failure. This is due to the fact that the cerebral arteriovenous oxygen difference does not always increase commensurately with the fall in cerebral blood flow. Whereas the hepatic and renal arteriovenous oxygen differences

increase 87 per cent and (about) 150 per cent, respectively, during heart failure, the cerebral arteriovenous oxygen difference increases only 41 per cent. (Table III.) The normal arteriovenous oxygen differences for these organs vary widely, being 6.1, 4.5 and 1.5 volumes per cent for the brain,[2] liver[8] and kidney,[10] respectively. It may be that the brain has difficulty in extracting oxygen after the venous tension falls below a given level. What determines the limits to which oxygen can be extracted by the brain under various circumstances is as yet unknown. In the present group of cardiac patients the mean cerebral venous oxygen tension was 25 mm. Hg. It is not known whether still further reduction in cerebral blood flow would result in cerebral venous blood of lower oxygen tension or whether rapid deterioration in cerebral function would follow if this point were passed. The study of cerebral metabolism in the high altitude chamber offers one approach to the problem.

TABLE III
COMPARISON OF MEAN ARTERIOVENOUS O_2 DIFFERENCE INCREASES IN VARIOUS ORGANS IN HEART FAILURE

	Normals	Cardiacs	Increase %
	Vol. %		
Hepatic A-V O_2 difference*	4.5	8.4	87
Mixed A-V O_2 difference*	3.9	7.1	82
Renal A-V O_2 difference†	1.5	3.7	146
Cerebral A-V O_2 difference	6.1	8.6	41

* Data obtained from Myers.[8]
† Data obtained from Merrill[9] and Cargill.[10] See text for explanation.

It is not difficult to understand, in view of the above findings, why an occasional cardiac patient develops mental symptoms. One can postulate that in such individuals cerebral blood flow is reduced so greatly that the brain cells are incapable of extracting sufficient oxygen to supply their demands; oxygen consumption falls strikingly and alterations in mental status occur. This same series of events has been shown to occur in cerebral vascular disease[11] in which the mechanism of reduction in cerebral blood flow appears to be the increased resistance to blood flow offered by the diseased cerebral vessels. Unfortunately, the present study did not include patients with abnormal mental status related to heart failure and definite conclusions concerning the reasons for mental changes in heart failure must await such investigation.

SUMMARY AND CONCLUSIONS

1. The mean cerebral blood flow in sixteen observations on fourteen subjects with heart failure was 39 per cent less than the mean for normal young subjects.

2. Although the mean increase in the cerebral A-V oxygen difference of the patients with congestive failure was 41 per cent over that for normal subjects, the mean cerebral oxygen consumption was reduced significantly below the normal value. Cerebral glucose utilization was also reduced.

3. Cerebral vascular resistance was increased 100 per cent over the normal.

4. Comparison of these data with available information on the mean change in cardiac output occurring in heart failure shows that the reduction in cerebral blood flow is proportional to the reduction in cardiac output.

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Treatment of Paralysis Agitans with Dihydro-beta-erythroidine*

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PARALYSIS agitans is a disturbance which manifests itself by muscular rigidity often associated with a tremor. The muscular rigidity is usually the most characteristic symptom and presents itself by a marked slowness of movement and a slow hesitating speech. Generally this disease is slowly progressive over an extended period of years. If not handled properly, it will lead in many cases to early and complete invalidism.

Treatment of these patients is a combination of intelligent use of drugs, exercise and emotional readjustment. Since at the present time there are many drugs which greatly aid in reducing the rigidity of these patients, drug therapy has for years been the prime consideration of the physician. As a rule the drugs available are more successful in treating the rigidity than the tremor. Since patients vary tremendously in their tolerance to taking these drugs, the therapy must be highly individualized to obtain maximum results. The principal drugs that have been used to date consist of atropine derivatives whose pharmacologic action is somewhat similar (hyoscine hydrobromide, rabellon, vinobel and bellabulgara). When these drugs are administered properly, most patients with paralysis agitans obtain considerable improvement from their rigidity. However, the amount of such improvement will vary from patient to patient and generally reaches a certain maximum beyond which it is usually impossible to go. It is therefore believed to be of value to report our experiences with a new compound having a curare-like action which when given in combination with the aforementioned atropine drugs generally produces augmentation of the improvement of the patient and has in our experience proven of distinct value in the treatment of paralysis agitans. This drug is known as dihydro-beta-erythroidine.

The natural source of this drug is from a genus of trees and shrubs (Erythrina L.) which is widely distributed over the tropics and subtropics of the entire globe. In the western hemisphere this shrub is found particularly in Central and South America. In the latter part of the nineteenth century it was noted that extracts of seeds of this plant were capable of paralyzing animals. In 1935 Ramirez and Rivero[1] reaffirmed the curarizing action of this drug. In 1937 Folkers and Major[2] isolated an alkaloid, erthyroidine, from a variant of Erythrina L. (Erythrina americana Mill) plant. This alkaloid consisted of a mixture of at least two isomeres, alpha- and beta-erythroidine. Of these beta-erythroidine was most readily obtained in the pure state and possessed more curare-like properties. This alkaloid was first used clinically in 1935 by Burman[3] in the treatment of spastic dystonia. Williams[4] in 1941 used large oral doses in a series of patients with spasticity of both pyramidal and extrapyramidal nature. One of his patients had paralysis agitans of twelve years' duration and in this case he noticed a marked decrease in the rigidity, with the tremor being unaffected. A similar beneficial result was reported by Harvey[5] in the following year. A disadvantage of this alkaloid was its brevity of action. In 1944 Unna and his colleagues[6] first reported on the action of a hydrogenated derivative of

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beta-erythroidine, namely, dihydro-beta-erythroidine. This drug proved experimentally to be six times as potent and its duration of action was considerably longer. Dripps and Sergent[7] administered this drug intravenously to 215 patients receiving general anesthesia and reported that the effect on the neuromuscle junction was indistinguishable from that of curare. In view of the suggestion that this drug might have definite beneficial results in the rigidity of paralysis agitans it was believed desirable to assess its value in a large series of patients with paralysis agitans followed in our clinic over a period of many years and already given the various other atropine derivatives for alleviation of their symptoms. The fact that these patients had all been under treatment for a considerable period of time under standard conditions enabled us to set up a base line upon which to judge the action of this new product.

TABLE I

1. Time taken to dress
2. Ability to comb hair
3. Ability to wash
4. Ability to shave
5. Ability to clean teeth
6. Ability to get in and out of a chair
7. Distance the patient is able to walk
8. Ability to write
9. Time taken for an average meal
10. Ability to hold and read a newspaper
11. Other evidence of improvement

PRESENT STUDY

Twenty-four patients with paralysis agitans received oral administration of dihydro-beta-erythroidine. The patients studied were classified in the following three main groups: Group I in which the drug was used alone without any of the atropine compounds; group II in which the drug was used alone initially but in which subsequently one of the atropine derivatives was added; group III in which both the dihydro-beta-erythroidine and atropine derivatives were administered concomitantly. In both groups II and III the dihydro-beta-erythroidine was withdrawn at frequent intervals after the patient had reached the point of maximum improvement in order to evaluate the effect of withdrawal of this drug upon the patient's symptoms. (Tables II, III and IV.)

The difficulty of evaluating any new drug in the treatment of paralysis agitans is always complicated by the psychotherapeutic effect of a change in medication upon the patient. Although this is definitely minimized in a large series of patients who have been followed for a long period of time by the same physician and who have been exposed to many different forms of medication, still it offers a definite complication in accurately assessing the specific benefits of any single drug. Since at the present time there are no objective methods of easily evaluating improvement in the rigidities and tremor of patients with paralysis agitans, a certain set of criteria had to be set down in order to offer some uniformity in objectivizing our observations. For this reason the criteria listed in Table I were used. As will be noticed in the table these

TABLE II

Case No.	Symptoms			Dosage in mg. of Dihydro-beta-erythroidine per Day	Additional Drugs	Treatment (days)	Toxic Symptoms	Results
	Age	Tremor	Rigidity					
1	70	+++	++	200	.....	28	Gastrointestinal distress, gaseous eructations	Poor
2	62	+++	++	100	Mebaral	14	Nil	Poor
				150	Mebaral	14		
				200	Mebaral	104		
3	65	+		150	.....	28	Anorexia, dizziness	Poor
				50	.....	28		

\+ Mild. ++ Moderate. +++ Severe.

criteria all had to do with the improvement of various functional activities of the patients, activities involving daily self-care and ambulation.

At the onset of our studies dihydro-beta-erythroidine was administered alone or along with a mild sedative such as mebaral. (Table II.) Only three patients were included in this group since the results were uniformly poor. It was soon apparent that dihydro-beta-erythroidine alone generally produces very few therapeutic effects in patients with paralysis agitans.

Five patients were started on dihydro-beta-erythroidine and after a period of 20 to 118 days one of the atropine derivatives was added to augment the effects of this medication. (Table III.) In two of these patients, Cases 7 and 8, the results were most gratifying and encouraged us to continue with our observations.

In the remaining sixteen patients dihydro-beta-erythroidine was administered concomitantly with or following the atropine derivatives. It is in this group that the best results were obtained. (Table IV.)

Ten of these sixteen patients showed very definite alleviation of symptoms. In order to determine the individual effects of the two medications dihydro-beta-erythroidine was discontinued for varying periods of time while the atropine derivatives were continued unchanged. In all these patients discontinuance of dihydro-beta-erythroidine for longer or shorter periods resulted in a definite recrudescence of symptomatology. Re-administration of the drug in each case again resulted in clinical improvement. In many of the patients removal of the drug produced such rapid and severe recurrence of symptoms as to produce violent protests on the part of the patient. Only those prolonged periods of removal of dihydro-beta-erythroidine are included in Table IV in order to simplify tabulation of our results. The shorter periods of removal have been purposely omitted. Repetition of this procedure in all these patients and the consistency of the picture resulting left no doubt in our minds that this particular drug is of great value in augmenting the beneficial action of atropine derivatives in paralysis agitans.

Oculogyric crises were not affected by this drug. It might be noted that this drug had very little effect upon the tremor and acted almost exclusively on the rigidity. As a result of our experiences with this medication we finally evolved the following procedure as offering the best therapeutic

TABLE III

Case No.	Symptoms			Dosage in mg. of Dihydro-beta-erythroidine per Day	Additional Drugs	Treatment (days)	Toxic Symptoms	Results
	Age	Tremor	Rigidity					
4	64	....	.....	250	.....	44	Nil	Poor
				100	Rabellon	100		
					Rabellon	73		
5	57	+	++	200	.....	59	Transitory dizziness	Poor
				200	Rabellon	76		
					Rabellon	96		
6	43	++	++	300	.....	56	Dizziness, disturbance of equilibrium	Poor
				200	Dial	29		
				200	Vinobel	56		
					Vinobel	200		
7	55	++	+++	200	.....	20	Nausea, vomiting	Good
				200	Vinobel	250		
8	64	+	++	200	.....	118	Nil	Good
				200	Rabellon	100		

+ Mild. ++ Moderate. +++ Severe.

results. Patients were first given one of the atropine derivatives and this drug was increased until the maximum benefits were obtained. Once a base line of improvement had been reached and maintained dihydro-beta-erythroidine was added. This drug was given orally in doses of 50 mg. four times daily. In most cases a definite additional improvement in symptoms was noticed within a week or two, the maximum benefits being reached within a month.

In spite of the fact that dihydro-beta-erythroidine has a curare-like action it is relatively non-toxic even in doses as high as

TABLE IV

Case No.	Symptoms			Dosage in mg. of Dihydro-beta-erythroidine per Day	Additional Drugs	Treatment (days)	Toxic Symptoms	Results
	Age	Tremor	Rigidity					
9	61		+++	250	Bellabulgara	50	Nil	Good
				100	.....	7		
				250	.....	26		
				250	Rabellon	372		
10	56		+++	...	Rabellon	720	Nil	Good
				200	Rabellon	180		
11	64	+	+	200	Rabellon	42	Nil	Poor
					Rabellon	120		
12	39	+++	++	200	Benzedrine Hyoscine	107	Nil	Good
		Oculogyric crises		200	Hyoscine	63		
13	52	+++	+	...	Vinobel Benzedrine	67	Mild anorexia, dizziness	Poor
				200	Vinobel Benzedrine	30		
14	54	+	+++	...	Rabellon	360	Transitory nausea and vomiting	Good
				200	Rabellon	270		
15	53	++	++	...	Rabellon	360	Slight nausea	Good
				200	Rabellon	270		
16	55	+++	++	...	Vinobel	200	Severe nausea and vomiting; drug stopped	Poor
				100	Vinobel	7		
17	72	++	+++	...	Rabellon Quinine	100	Nil	Good
				200	Rabellon Quinine	210		
18	58	++	++	...	Rabellon Quinine	100	Nil	Good
				200	Rabellon Quinine	210		
19	56	+++		200	Rabellon Benzedrine	40	Nil	Poor
		Oculogyric crises			Rabellon Benzedrine Phenobarbital	20		
				200	Rabellon Benzedrine	110		
20	66	++		200	Rabellon	14	Blurring of vision; dizziness	Poor
21	58	++	+++	...	Vinobel	100	Nil	Good
				100	Vinobel	300		
22	48	+	++	250	Rabellon	288	Nil	Poor
				200	Rabellon	70		
					Rabellon	60		
23	60		+++	200	Vinobel	200	Nil	Good
24	46		+++	...	Hyoscine	460	Nil	Good
				250	Hyoscine	200		

+ Mild. ++ Moderate. +++ Severe.

300 to 400 mg. daily. The toxic symptoms generally consist of gastrointestinal disturbances, blurring of vision and dizziness. Only the first of these is of any importance and consists of mild anorexia, nausea, vomiting and gaseous eructations.

CASE REPORTS

CASE I. E. P., a fifty-six year old male, first noticed difficulty in walking due to stiffness in his right leg six years before being observed in the clinic. This stiffness was soon followed by an aching in the back and some difficulty in the use of both hands. At this time a diagnosis of paralysis agitans was made and the patient was given a variety of medications. He was seen in our Neurology Clinic in May, 1947, at which time he had a typical wiped-out facies, a cog-wheel rigidity of the upper limbs and marked stiffness of all four limbs, with excessive sweating. His rigidity was so severe that he was unable to care for himself and had great difficulty walking.

He was given rabellon and the dose was gradually increased until he was taking 10½ tablets daily. With this medication the patient noted definite improvement in his condition. He was now able to shave himself, although with difficulty, and could slowly dress himself. He was also able to walk about unassisted. Dihydro-beta-erythroidine was started on December 4, 1947. Following institution of this drug further improvement was immediately noticed. The patient's ability to walk increased markedly so that within a few months he was able to walk two to three miles. The decreased rigidity in his upper limbs was so striking that he was now able to pull his sweatshirt over his head. On February 12, 1948, dihydro-beta-erythroidine was discontinued for seven days. Even during this short period the patient's rigidity increased. He developed soreness and stiffness in the muscles of his back and his ability to shave became definitely impaired. He was again given dihydro-beta-erythroidine with immediate improvement. When seen on September 7, 1948, this patient in comparing his condition during the summer of 1948 with that of 1947 commented that the past summer was the first time in two years that he was able to cast while fishing.

CASE II. W. S., a fifty-five year old male, was first seen on October 19, 1945, with very severe paralysis agitans. At that time he was unable to dress, sit or shave himself. He required aid in getting in and out of bed. Examination revealed typical paralysis agitans. His facies was immobile, rigidity was marked and there was a mild tremor involving the upper extremities. His gait was difficult and propulsive in nature.

From October, 1945, until January, 1948, the patient was placed on vinobel taking as many as fifteen tablets daily. Even with this medication he showed very little improvement and remained more or less completely invalided because of his severe muscle rigidity. In January, 1948, the medication was supplemented with 200 mg. of dihydro-beta-erythroidine daily. During the first few days he noticed some nausea and vomiting. Physically he showed a rapid and dramatic improvement. He soon became able to feed and wash himself although he still required some help in getting in and out of bed. In October, 1948, the patient was transferred to another hospital where dihydro-beta-erythroidine was not available. Within a week his condition again deteriorated to a state of complete invalidism. Improvement again followed re-administration of dihydro-beta-erythroidine. On three subsequent occasions when supply of the drug was temporarily not available complete relapse occurred. On three separate occasions without the knowledge of the patient placebos were substituted for dihydro-beta-erythroidine. On each occasion the patient's condition regressed and the patient almost immediately recognized the difference in the action of the medication.

CASE III. G. B., a fifty-four year old male, first noticed a slowing of his movements and difficulty in the use of his left hand about fourteen years prior to admission to the hospital. There was a gradual progression of the illness which soon became associated with mild tremor involving the right upper extremity. Throughout these years his condition continued to progress. His gait became more involved and when he was hospitalized and first seen in January, 1948, he had deteriorated to a state of almost complete invalidism. He walked with a festinating gait and great difficulty. It was an effort for him to rise from a chair or to feed himself.

The patient was placed on rabellon therapy and showed only slight improvement. Even on large doses of this atropine derivative he was unable to walk to the dining room or to care for his daily needs. In January, 1948, the therapy was augmented by 200 mg. of dihydro-beta-

erythroidine daily. Within a few days the patient subjectively expressed a feeling of greater strength and well being. Within a few weeks there was definite loss of rigidity in his shoulder, leg and neck muscles. He was now able to feed himself and to get out of bed without assistance. He was able to walk to the dining room and to care for all his daily needs. His speech became much more distinct and understandable. There was no change, however, in the patient's tremor. On several occasions an attempt was made to substitute placebos for the dihydro-beta-erythroidine but this change was immediately noticed by the patient because of the increasing symptomatology. This patient has now been carried on the combined rabellon–dihydro-beta-erythroidine therapy for 270 days and improvement has been maintained throughout this period.

Case IV. F. K., a sixty-one year old male, was well until 1935, at which time he first noticed symptoms of paralysis agitans consisting of rigidity followed by tremor involving first the hands and then the lower extremities. There was gradual progression of his symptoms so that he was forced to discontinue his work in 1936. During the eight years prior to his initial hospitalization in January, 1946, he had been treated with atropine, quinine, hyoscine, rabellon and other drugs without appreciable effect. On admission to the hospital the patient was unable to raise himself out of a chair and complained of severe generalized muscular pain. He was unable to walk without assistance. His speech was slow and difficult to understand. He was unable to shave himself and eating was a slow laborious process.

On admission to the hospital he was placed on bellabulgara and dihydro-beta-erythroidine concomitantly. Bellabulgara was begun at three tablets daily and increased to fifteen tablets a day. Dihydro-beta-erythroidine was started at 60 mg. daily and gradually increased to 250 mg. per day. On this combined drug therapy his rigidity decreased markedly and for the first time in many years he was able to walk about and shave himself. Both these medications subsequently became unobtainable due to the onset of the war so the patient was placed on rabellon with a resultant gradual deterioration in his condition. In August, 1947, the patient was again started on dihydro-beta-erythroidine, receiving 100 mg. per day. This dose was gradually increased to 250 mg. per day. Improvement again resulted. He began to walk unassisted and for the first time since discontinuance of the combined medication was able to climb stairs. His speech was improved. On numerous occasions dihydro-beta-erythroidine was deliberately discontinued for short periods but this absence of medication was immediately reflected in the patient's increased rigidity and definite limitation in activities. This patient has now been maintained on combined rabellon–dihydro-beta-erythroidine therapy for 372 days. His improvement has been maintained and he is now able to carry on with facility most of his personal activities and is still able to walk unassisted and go up and down stairs.

Case V. A. N., a forty-three year old male, first noticed development of his symptoms nine years before admission to the hospital. At this time he noticed a mild tremor in his right hand which progressed to involve all four extremities and was soon associated with a moderate rigidity. Early in the course of his illness he was placed on rabellon therapy from which he obtained definite relief with improvement in all his symptoms. He continued on this medication during the next four years and then changed to stramonium.

When seen in 1947 there was a gross tremor of the right hand and moderate rigidity of all the musculature. Speech was slow and his face had a typical mask-like facies. In July, 1947, the patient was placed on 100 mg. of dihydro-beta-erythroidine therapy per day. In spite of his medication his condition continued to go downhill. Walking became more difficult, speech slower and writing more unintelligible, forcing him to discontinue his work. Dihydro-beta-erythroidine was increased to 200 mg. daily without any effect. When seen on September 11, 1947, he had shown a progressively downhill course. He was now unable to write. He was much more rigid and his ability to walk had decreased. At this time vinobel was added to the therapy. During the next few months his condition improved somewhat. His talking and walking were better and subjectively he was much improved. Improvement continued until December, 1947, at which time dihydro-beta-erythroidine was discontinued. Discontinuance of this medication made no difference in the patient's general condition. He continued to do as well on vinobel alone as he had been doing on the combined vinobel–dihydro-beta-erythroidine therapy. This patient has now been on vinobel therapy alone for 200 days.

COMMENT

Twenty-four patients suffering from paralysis agitans were treated orally with a relatively new curarizing agent, dihydro-beta-erythroidine. These patients received an average dosage of 200 mg. daily. When this drug was used alone, it proved to have little or no effect upon the symptomatology. However, when used as an adjunct to the atropine derivatives, there was striking improvement in most cases in which rigidity was a feature. This drug had little effect upon the tremor or upon the oculogyric crises.

The toxic symptoms from dihydro-beta-erythroidine consisted primarily of gastro-intestinal manifestations, visual disturbance and some dizziness. These toxic symptoms appeared in eleven patients but were for the most part mild and transitory and in only one case necessitated discontinuance of medication. This new drug when administered orally appears to have no effect upon the blood pressure and results in no other systemic manifestations.

Although our series is still small, the results are very encouraging and would suggest that this medication offers excellent possibilities as an adjunct to the therapy of paralysis agitans.

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Use of Curare in the Treatment of Anterior Poliomyelitis*

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DURING the last decade considerable attention has been devoted to the treatment of muscle spasm, tightness or shortening of affected muscles in patients with acute anterior poliomyelitis. This symptom generally has been treated with some form of heat, either moist[1,2] or dry.[3–5] Hot fomentations (packs)[6] or hot water (tub baths, Hubbard tank or pool therapy)[7–9] have been the usual methods of applying moist heat; radiant heat lamps, light cradles, infra-red or luminous bakers have been used to supply dry heat. Artificial fever has also been employed as a form of thermotherapy.[10] It has been generally observed that application of heat provides considerable relief to the patient during the acute stage and many hold the opinion that repeated applications of hot packs cause muscular relaxation, reduction in muscle tenderness and lengthening of the shortened muscle.

Evidence has accumulated that at least some of the muscle tightness is caused by heightened irritability of myotatic reflexes resulting from lesions in the brain stem[11–14] although it also seems quite possible that the pathologic site responsible for a portion of the muscle tightness may be located within the muscles or at the neuro-muscular junction.[15] However, the latter hypothesis requires substantiation.

Recently, increased interest in antispasmodic drugs has developed in the hope that useful agents may be found to produce muscular relaxation of tightened "polio" muscles. One of these substances, known as beta-erythroidine, has been studied by Schwartz.[16]

The use of curare has been advocated by Ransohoff[17] who reported rather spectacular results in the treatment of poliomyelitis patients given this drug. Reasons for advocating its use may be summarized as follows: (1) to relieve spasm in the acute stage; (2) to aid in preventing shortening in weakened muscles; (3) spasm is deleterious to the muscle. He noted relief of muscle tightness of the neck, back, knee flexor and plantar muscles as well as of pronator and intercostal muscles. He also noted restoration of the ability to swallow within a short time after administration of the drug. His system of treatment consisted of intramuscular injections two to three times daily of a standardized extract of curare known as intocostrin, followed by vigorous active and passive movement of involved muscles. Beneficial results reported following this treatment were so impressive that we decided to try it in some selected patients.

Observations on the use of intocostrin in treating acute anterior poliomyelitis began August 17, 1946. Only patients showing severe muscular tightness or severe bulbar symptoms, evidence of intercostal or laryngeal spasm, or having great difficulty in synchronizing their breathing with the respirator were selected for study. Owing to the severity of the epidemic and to the great demand made upon available personnel for administering routine treatments it was not possible to set up a well controlled research program. More extensive observations will be required before attempting to pass any final judgment on the merits of curare in handling acute poliomyelitis;

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controlled observations in a large number of cases and accurate statistical analysis of the data obtained must be made in order to evaluate the procedure adequately. However, a sufficient number of patients were treated by us to become familiar with the method and to form clinical impressions regarding the response of patients to curare therapy.

The treatment program consisted of administering curare more or less in accordance with the dosage procedure advocated by Ransohoff,[22] namely, 0.9 to 1.5 units of intocostrin per kg. of body weight two or three times daily. Physical therapy, consisting principally of passive stretching combined with or followed by active assistive exercises for twenty to forty minutes, was carried out immediately following each injection. A maximum patient load of three patients to one physical therapist was followed. Muscle re-education, accurate measurements of the range of motion of joints and frequently recorded progress notes were made by the physical therapists during the course of treatment. Ample precautions were taken to cope with respiratory emergencies which might have arisen following injections and additional interns and residents were assigned to patients receiving curare therapy.

OBSERVATIONS

Careful studies were made of forty patients treated with the intocostrin and physical therapy program. Twenty-three of this group were males and seventeen were females. Ages ranged between two and thirty-four years. There were sixteen patients between the ages of one and ten, eleven between ten and twenty, nine between twenty and thirty and five between thirty and forty. All patients except the five respirator cases showed severe tightness of the neck, back and hamstring muscles, and approximately 25 per cent showed varying degrees of opisthotonos. Other muscles, such as the gastrocnemius-soleus, pectoralis major, latissimus dorsi, subscapularis, quadriceps femoris, biceps femoris, semi-membranosus and semi-tendinosus, flexor muscles of the fingers and toes, plantar flexors of the foot, external and internal rotators of the hips and shoulders, pronators and supinators of the forearm and abdominal muscles were involved in varying degrees in various patients. Approximately 30 per cent of patients showed muscle tightness only whereas the remaining 70 per cent showed varying degrees of paresis and paralysis. Our chief interest in using intocostrin was to observe its effects on these tightened muscles. Repeated measurements of the range of motion of joints were made before and after each treatment. Repeated tests were made to evaluate the power of muscles at approximately two-week periods.

Eleven patients, or 27½ per cent, were discharged directly to their homes apparently symptom-free at the end of the quarantine period (two weeks). Of these, two patients, or 5 per cent, subsequently developed muscle paresis accompanied by muscle soreness and tightness of the back and hamstrings; both were re-admitted for further treatment. A number of patients were discharged to other hospitals and were lost to further observation. The remainder of these patients was transferred to Unit 1 in the Los Angeles County Hospital where additional observations and treatments were made for periods of one to three months. Six patients, or 15 per cent, showed only slight or no significant improvement with intocostrin and physical therapy treatment. Severe localized pain developed suddenly and spontaneously in the muscle and soft tissues in and about the joints of six patients receiving intocostrin. This pain was constant, sharp and severe in character and was augmented greatly by active or passive stretching or by deep palpation. Two patients developed unilateral pain in the knee; two developed pain in the upper dorsal region of the back; one developed bilateral pain in the hip joints and surrounding soft tissues involving the upper part of the adductor, the rectus femoris and the hip rotators (pain was much more severe on the left than on the right) and one patient

developed pain in both heels extending up to the tendo-Achilles and the lower part of the soleus muscle. Those patients exhibiting pain in the heels and in the hips showed prompt disappearance of the pain when the injections were discontinued. Whether or not a causal relationship existed between intocostrin and the development of pain in these patients cannot be said with certainty but presumptive evidence exists that the pain was related in some way to the therapy. In some, these symptoms disappeared promptly after discontinuing the injections whereas in others seven to ten days were required for it to disappear. Hot packs were used with comfort in patients exhibiting severe pain. No patient showed any residual pain at the time of discharge from the hospital.

CASE REPORTS

CASE I. D. C., age six. The chief complaints were headache, neck and back pain, general weakness, anorexia, somnolence for thirty-six hours and dysphagia for twenty-four hours. The patient awoke with severe frontal headache and some neck and back pains. There was a temperature of 99°F. and anorexia. Throughout the day the patient was somnolent and complained of general weakness. An enema failed to relieve constipation of several days' duration. In the evening the patient complained of difficulty in swallowing but there was no regurgitation through the nose. The child was seen by a physician on the following afternoon who found diminished reflexes and a stiff neck and referred the patient to the Los Angeles County Hospital.

Upon physical examination it was seen that the patient was an alert child able to walk and stand without assistance. There was no visual disturbance or hoarseness. Weakness of the right palate with deviation of the uvula to the right as well as right facial weakness was present. There was 2+ neck, back and hamstring tightness but no apparent weakness. Spinal smear revealed occasional lymphocytes. No growth appeared on culture. Total protein was 39 mg. per cent and the Pandy test was negative. Blood count was white blood cells, 10,050; polymorphonuclears, 77 per cent; lymphocytes, 23 per cent; packed cell volume, 43 per cent.

On the first day the patient was fed by a Levine tube. Catheterization of the bladder was necessary. An increase in neck extensor tightness was noted. No weakness was seen. The patient was listless but cooperative. Four hot packs were applied in twenty-four hours. On the following day respirations were shallow and rapid; mucus accumulating in the throat required aspiration and the tightness was not relieved. Packs were given throughout a twenty-four-hour period. On the next day opisthotonos had occurred. The patient's head deviated to the right and was held rigidly. It was resistive and painful when an attempt was made to bring it to the midline. The palate was flaccid and deviated to the right. There was no weakness. Deep reflexes were absent. Curare, 1.1 cc., (first day of curare) was administered. Severe tightness persisted on the fourth day. Dysphagia was complete and frequent aspirations were necessary. Penicillin 20,000 units, every three hours were administered intramuscularly for nine days. Six Kenny packs were used as well as one injection of 1.1 cc. curare. On the following day 1.1 cc. curare was given twice and 1.8 cc. once. The patient was more alert and could be moved without pain. There was marked diminution in the tightness of the neck and hamstrings. Opisthotonos was relieved. On the seventh day the patient began to show more interest and fair color was present. Curare, 1.8 cc., was given twice. Curare, 1.8 cc., was given three times daily starting on the tenth day. Hamstrings were extended to 50 degrees and to 105 degrees with the legs over the edge of the bed. On the thirteenth day 1.8 cc. curare was given three times daily. The Levine tube was removed. The temperature was normal and the facial weakness was slight. Extension was back to 120 degrees with the knees over the edge of the bed; the hamstrings extended to 75 degrees. The patient was active in bed. On the twenty-first day the patient's general well being was excellent. There was only slight facial weakness and very mild neck, back and hamstring tightness. The patient could touch his toes with his fingers, standing in a straight leg position. Mild weakness was discovered in the right quadriceps. Curare was discontinued. A total of fifty-one doses had been given. The patient was discharged on the thirtieth day.

CASE II. N. H., aged seven. The chief complaints were frontal headache of three days' duration, mild fever, soreness of the anterior neck muscles and swelling of the glands of the neck. The patient was unable to sit up by herself because of muscle weakness and she complained

of generalized muscular soreness and extreme weakness of the muscles of the right arm. The patient was perfectly well until ten days before admittance to the hospital when she developed a frontal headache which lasted for three days. Three days later she noticed some soreness of the anterior neck muscles and a doctor was called. Examination showed a mild fever and some enlargement of the lymph glands of the neck. Extreme weakness of the back muscles developed seven days prior to admission and the patient was not able to sit up since the onset of this weakness. For the past five days the patient complained of generalized muscular soreness, accompanied by extreme weakness of the muscles of the upper right extremity. She noticed some stiffness and pain in the muscles of the neck during this period. At no time during the illness was the patient nauseated and she did not vomit. Slight anorexia was present during the first three days of illness. She has had no photophobia, difficulty in eating or drinking and no difficulty in breathing. No changes in voice and no diarrhea or constipation were present.

Physical examination revealed a somewhat lethargic, apprehensive, white female child who appeared quite ill. The skin was pale and the facial expression was drawn. The patient was unable to sit up and there was no apparent movement of the muscles of the right upper extremity. Reflexes were absent from all extremities and the abdominals were absent. Kernig's and Brudzinski's signs were positive. Laboratory findings showed the following: Spinal fluid, clear; cells, 74, lymphocytes, 100 per cent; Pandy 1; sugar, ten drops reduced 5 cc. of Benedict's solution. Blood: white blood cells, 8,100; differential, 52 per cent polymorphonuclears; lymphocytes, 48 per cent; packed cell volume, 42 per cent. A diagnosis of acute anterior poliomyelitis, spinal paralytic type, was made.

On the first day the polio regimen was started. Prone packs were applied with supplementary packs to the neck, thighs and shoulders. Continuous packs were applied to the chest. The pack regimen was continued on the following day. The patient appeared considerably more comfortable but she complained of pain in her right arm. The spinal fluid had a ground-glass appearance and was slightly cloudy; smear, cellular débris; occasional lymphocytes, no organisms; Pandy, faint trace; chlorides, 780; total proteins, 109. On the next day the muscle tightness continued essentially the same. The patient was non-cooperative and complained of severe pain in the hamstrings, abdominals and neck extensors. She lay on her side or on her back with her knees markedly flexed. The pack regimen was continued. There was slight improvement in tightness and muscle tenderness the next day and moderate weakness in the muscles of all extremities except the right upper which showed severe weakness. On the fifth day her condition was essentially the same. A bulging was noted in the intercostal areas on the right side of the thorax. The patient had had repeated nose bleeds for two days. The pack regimen was increased to seven packs a day.

Ninth Day—Curare treatment was started on the ninth day and the packs were discontinued. Following one day of treatment with curare and passive exercises a marked increase in the flexibility of the back and lower extremities occurred. The patient sat on the side of the bed; her back appeared somewhat rounded. Curare treatment was continued three times daily in a dosage of 1.6 cc. administered intramuscularly. On the fourteenth day the patient complained of severe pain in her right arm and a similar complaint was made on the following day; she was somewhat uncooperative. On the eighteenth day the extreme tightness and pain which were present before starting curare had entirely disappeared and on the twenty-fourth day the patient walked with support from the bed to the door and returned. The patient was receiving curare three times daily. On the twenty-seventh day curare was discontinued. The patient started on gait training and continued flexibility exercises; her condition remained essentially the same from October 1st to October 5th. On October 10th considerable tightness was noticed in the right pectoralis major, latissimus dorsi, both hamstrings and gastrocnemius muscles. Stretching and active resistive exercises were continued. On October 18th curare therapy was started again in a dosage of .9 cc. given intramuscularly twice daily. The dosage was increased to 1.6 cc. on October 22nd. During this time the patient developed extreme pain in the heels and calf muscles. Neither packs nor curare were effective in control of the pain. Curare was given three times daily without significant effect on the pain and muscle tightness of the hamstrings and the calf muscles. On November 1st pool therapy was started and curare was continued. On November 22nd.

following an injection of .7 cc. curare, the patient developed a severe reaction. Respirations became shallow and there was extreme weakness of all the muscles. She was given oxygen therapy and artificial respiration. The reaction started about five minutes after the injection. Recovery was complete in about twenty minutes and curare was discontinued. Examination on November 25th showed the patient unable to sit up unassisted. Flexibility of the trunk was essentially normal. There was residual tightness in the right hamstring, the left hamstring was essentially normal. The muscles of the right forearm and hand showed an increase in muscle power; the muscles of the arm and shoulder girdle showed extreme weakness. Therapy, consisting of pool therapy, gait training and muscle re-education, was administered for the next three weeks. On December 14th an increase in the power of the muscles of the right upper extremity was noted. Tightness of the adductors and marked weakness of the abdominals was still present; flexibility of the neck and trunk was normal. There was slight lordosis on standing and the left hip was higher than the right. There was instability of posture on standing. On December 24th flexibility was essentially normal. There was residual weakness of the muscles of the right upper extremity. The abdominals and left anterior tibial showed weakness. The patient showed marked improvement during the month of December. On December 30, 1946, the patient was transferred to another hospital for further treatment.

Case III. P. S., aged seventeen. Chief complaints were "cold" and low back pain of five days' duration; also fever, neck and hamstring stiffness on one day. The patient developed a "cold" and an associated low back pain five days before entry but worked at regular duty for the following four days. The day before entry the patient developed a mild fever, neck and hamstring tightness and some muscle tenderness.

Physical examination revealed the patient to be restless and tossing about. No muscle weakness was noted. There was a poker spine with 3+ neck and hamstring tightness and the patient complained of severe back pain and aching in the lower extremities. Spinal fluid examination: clear, colorless; white blood cells, 130; polymorphonuclears, 15 per cent; lymphocytes, 84 per cent; Pandy 1+. Benedict's solution reduced with 15 drops; chlorides, 760; protein, 112 mg. per cent; smear, few lymphocytes, occasional polymorphonuclears; culture, no growth. Blood: white blood cells, 9,000; lymphocytes, 40 per cent; packed cell volume, 44 per cent.

On the first day one injection of 2.7 cc. intocostrin (curare) was given. Only slight weakness of sternomastoids and the right shoulder group were noted. The following day 2.7 cc. intocostrin were given at midnight and 4 cc. in the morning and afternoon. There was increased range of motion in almost all the joints. The patient stood for about five minutes. The next day 4 cc. intocostrin were given three times in twenty-four hours. There was almost a normal range throughout this period. Slight neck stiffness was noted. Intocostrin, 4 cc., was given three times on the next day. The patient stood and walked. There was slight stiffness in the neck, back and left hamstring muscle. The patient did twenty push-ups and touched his toes seven times while standing. On the tenth day the range was completely normal and intocostrin was discontinued. On the fourteenth day slight right lumbodorsal scoliosis was noted but there were no weakness, tenderness or tightness. A five-month check-up showed slight hamstring tightness but the patient has been working full-time with no complaints.

Case IV. H. C., aged twenty-nine. The chief complaints were back pain, severe headache, dysphonia and difficulty in breathing. The patient was perfectly well until the evening of August 19, 1946. She had a headache, stiffness and soreness of the back. The back symptoms became increasingly worse, beginning in the low back and involving the dorsal region. On August 20th she vomited four times and felt nauseated thereafter. Anorexia developed the first day of illness. The patient became constipated and her fever remained around 100°F. She noticed some weakness of the joints on August 21st and she also had difficulty in breathing, being unable to respire deeply by chest movement; she could breathe satisfactorily by means of abdominal breathing. The patient was unable to urinate or defecate after the onset of symptoms. She was admitted to the hospital August 21, 1946.

Physical examination revealed a well developed white female who showed some difficulty in breathing and exhibited considerable difficulty in moving. She resisted being moved or disturbed. She complained of nausea, severe headache and backache. Marked tightness,

tenderness and stretch pain were present in the posterior neck muscles, back and hamstrings. Tendon reflexes were extremely sluggish and abdominals were absent. Laboratory findings revealed the following: spinal fluid, ground glass, colorless; cells, 900; polymorphonuclears, 45 per cent; monocytes, 55 per cent; + Pandy; sugar, normal. Blood: white blood cells, 11,400; polymorphonuclears, 88 per cent; monocytes, 12 per cent; hemoglobin, 16.5 Gm. A diagnosis of acute anterior poliomyelitis with spinal and respiratory involvement was made.

The following day routine pack therapy was started. Continuous chest packs were applied. The patient was catheterized as she was unable to void. The next day difficulty in breathing developed at 4:30 A.M. Chest packs were increased. Severe weakness of the anterior neck muscles developed as well as marked weakness of the muscles of the shoulder girdles, the triceps, pronators, hip flexors, adductors and abductors, quadriceps and hamstrings. Hot packs were continued for the chest and extremities. Curare therapy was started at 4:30 P.M. the next day; 2.3 cc. were injected intramuscularly. Following curare treatment combined with flexibility exercises the flexibility increased in the hip flexion from 30 degrees to 70 degrees. Two injections of curare were given the following day. It was still necessary to catheterize the patient. On the sixth day two injections of curare were given; 3.9 cc. were injected.

The patient was still very restless and very uncomfortable. There was slight reduction in the pain and tightness of the muscles of the shoulder girdle. A midnight injection of curare was added to the treatment the next day. There was still considerable pain and tightness and the patient was hypersensitive to movement. Tightness remained unchanged. On the eighth day 3.9 cc. curare were given. No significant change was noted. Some return of active movement of the muscles of the legs developed with more improvement of the left than the right. Tightness of the thighs returned in the afternoon and persisted during the evening. After each injection of curare the pain and discomfort seemed to be relieved. The patient sat up to 90 degrees with her legs over the edge of the bed. Curare therapy was continued the next day; tightness was approximately the same. Hip flexion was accomplished with the knees straight to 60 degrees. Movement over the right upper extremity produced pain in the posterior deltoid. Tightness in the remaining muscles was about the same. Continued curare injections were given three times a day. The patient sat up to 100 degrees with her legs over the side of the bed. There was marked weakness in the upper and lower extremities, also in the anterior, posterior, neck and abdominal muscles. There was severe tightness in the neck, back and hamstrings and gastrocnemius muscles and the abductors and adductors of both legs. There was apparently no difficulty in breathing or swallowing. Speech appeared to be normal. On the eleventh day 3.9 cc. curare were injected three times daily. Spasm was about the same. The patient still had a great deal of pain and difficulty and backache still continued. She seemed quite apprehensive and resisted flexibility exercises more so than any of the other patients. Her shoulder was still painful but she had full range of motion.

Curare and passive flexibility exercises combined with tolerance-stretching were continued three times daily during the next month without any significant change. September 28, 1946, curare was discontinued and muscle re-education exercises and gait training were started. The patient sat up about one hour. Generalized muscle stretch had increased. The patient's mental outlook was excellent. Hamstring tightness improved to approximately 85 degrees flexion during the last month of curare therapy. Muscle re-education and gait training were continued until the patient was transferred to another ward on October 18, 1946. It was noted at the time of transfer that the patient was still unable to turn over in bed by herself but was able to sit up with support and to walk with assistance. She was able to comb her hair and had recovered considerable power in the muscles of both upper and lower extremities. On October 10th pool therapy was started twice daily followed by bobbing exercises, active assistive and resistive exercises, gait training and occupational therapy. This treatment was continued during the month of October. On November 2nd the patient was able to turn over in bed unassisted but was unable to sit up without assistance. On November 10th she was able to sit up in bed by herself.

Examination on December 23rd showed normal flexibility of the neck and upper extremities. There was some atrophy of the muscles of the thenar eminence, more on the left than on

the right. Both triceps were weak. Slight weakness of the wrist flexors and extensors was noted. There was some atrophy of the interosseus muscles of the right hand and there was extensive weakness of the abdominal muscles, more on the right than on the left. Hip flexors were weak, more on the left than on the right. There was marked improvement in the strength of the quadriceps; the left was considerably stronger than the right. There was marked weakness of both hip abductors and moderate weakness of the left adductors; there was marked weakness on the right. Straight leg raising to 75 degrees on the right and 65 degrees on the left; there was slight tightness and stretch pain of the right rectus femoris muscles. Marked weakness of the right and moderate weakness of the left hamstring muscles were noted with residual tenderness on deep palpation of both calf muscles. Treatment program continued essentially the same until February 14, 1947, when the patient was discharged from the hospital with instructions for home treatment and told to return to the out-patient clinic for follow-up care. Several electromyographic examinations of the muscles of the upper and lower extremities were made during the course of treatment. On April 2nd the patient showed continued improvement and was discharged from the hospital service. She is now able to walk unassisted with the aid of crutches.

CASE V. C, S., aged thirty-three. The chief complaints were headache and backache of twenty-eight hours' duration. The patient was well until one week previously when severe headache and backache developed lasting twenty-four hours. The patient was quite well until twenty-eight hours prior to admittance when these symptoms recurred with fever up to 100.4°F. The patient then noted aches in the thighs, a stiff neck and mild nausea. No respiratory, urinary or bowel symptoms were noted.

Physical examination revealed the following: temperature, 99°F.; neck, 3+ tightness; back, 4+; hamstrings, 2+; slight weakness of the sternomastoid; reflexes slightly diminished. Spinal, ground glass; 465 cells; 98 per cent round cells, Pandy 1+. Blood count, 10,500; 72 per cent polymorphonuclears; packed cell volume, 41.

On admission rigidity of the neck, back and hamstrings was now severe. Prone packs were applied throughout the day. The following day 2.5 cc. intocostrin (curare) were given once and 4.4 cc. were given once. Relaxation was marked following injections; the patient became optimistic and cheerful over the results. The next day 4.4 cc. intocostrin were given three times. The patient was now able to touch his toes and place his head between his flexed knees. Hamstring muscles were still tight. The patient was much more comfortable. On the fourth day 4.4 cc. intocostrin were given three times. Relaxation continued but the patient required stretching following the injections. The next day 4.4 cc. intocostrin were given twice. The patient was limber at all times without relapsing into degrees of rigidity and could reach beyond his toes. The patient could sit erect without difficulty with a 90 degree range of motion of his neck. Intocostrin was discontinued on the sixth day and on the twelfth day the muscles were completely flexible and there was no weakness or tenderness. There was slight right lumbar left dorsal curve. The patient was discharged.

RESPIRATOR PATIENTS

A total of ten patients received intocostrin during treatment in the respirator. Four made satisfactory recovery and six did not. Autopsies were performed on three of the six. None of the patients autopsied showed any gross or microscopic evidence indicative of toxic reaction to the drug. Intocostrin was found to be most valuable in the early phases of those respirator patients not coordinating their breathing with the respirator. It stopped aberrant irregular impulses from coming through to the intercostals and diaphragm and the patient's breathing assumed the rhythm of the respirator. It was the opinion of the attending staff that relief of laryngeal and intercostal tightness by intocostrin saved at least one patient and possibly two more from asphyxiation and also from subsequent pulmonary involvment. The airway became more patent and was accompanied by subsequent improvement in the drainage of mucus from the trachea and bronchi. One of these patients was removed from the respirator in thirty-six hours when bulbar symptoms, as well as the rigidity of the neck, back and hamstring muscles had largely disappeared. Another patient was removed from the respirator after one week, following which

recovery was rapid and the patient returned to normal within two months.*

Sex	Age	Dose	Total Treatments in Hubbard Tank	Total Treatments in Pool
Female....	12	1¼ cc.	0	15
Female....	33	2½ cc.	0	13
Female....	26	2¼ cc.	0	7
Female....	9	1 cc.	4	12
Female....	10	1 cc.	4	17
Female....	9	1 cc.	0	16
Female....	36	2½ cc.	0	2
Male.....	26	2½ cc.	8	0

CONCLUSIONS

1. Patients showing severe symptoms consisting primarily of muscle tightness responded to intocostrin and physical therapy using the method of treatment suggested by Ransohoff.

2. Patients responding to intocostrin and physical therapy did best with prompt treatment, within two to six days after the onset of muscle involvement.

3. Patients showing a combination of severe muscle tightness and weakness were less likely to be benefited by curare than those showing chiefly muscle tightness alone.

4. Patients showing extensive paralysis and weakness apparently were not benefited greatly by curare treatment.

5. Localized pain, tenderness and soreness of the soft tissues in and about the joints were observed in 15 per cent of patients. Insufficient data are available to state definitely that these symptoms were caused by intocostrin injections.

6. The muscle tightness of some patients who were refractory to pack therapy was relieved by intocostrin and physical therapy.

7. A few patients (approximately 15 per cent) were quite refractory to either hot packs or curare therapy, in some instances both treatments being combined with no benefit.

8. Curare therapy is advantageous in treating certain respirator patients who show evidence of laryngeal or intercostal spasm, or who have difficulty in coordinating their respiratory effort with the rhythm of the respirator. It is advisable to reduce the dosage of curare in such cases.

* During 1948 the largest and most severe epidemic ever to occur on the Pacific coast occurred in Los Angeles. Due to shortage of personnel curare could not be used in the paralytic patients, being of no value when not accompanied by physical therapy.

However, in follow-up therapy of some of our patients, which the U. S. Naval Hospital at Corona so graciously undertook for us, curare was given twenty minutes before exercising patients in the Hubbard Tank three times daily or in the warm pool twice daily. Captain Edward Kenny's comment follows:

We have been using Squibb's Intocostrin containing 20 units per cc. equivalent to 3 mg. *d*-tubocurarine chloride pentahydrate with an initial dose of approximately 1 unit per Kg. and subsequently varying the dose slightly for optimal therapeutic effect. The drug is given intramuscularly between thirty and forty-five minutes before a session of physical therapy and in all except one patient a very significant reduction in muscle spasm and stretch pain was apparent.

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Myocardial Infarction*

I. Statistical Analysis of 679 Autopsy-proven Cases

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THIS presentation and the succeeding paper were undertaken with the purpose of studying the clinical picture of myocardial infarction, reviewed in retrospect from the autopsy table. By studying the material in this manner we hoped to accomplish the following: (1) a reasonably accurate statistical appraisal of the incidence by age, sex and race, as well as the location of the infarct and its complications in a large group of patients; (2) using this material as a sound guide, a diagnostic appraisal of the efficacy of the electrocardiogram and the clinical impression, "working backward" from the autopsy table. From the work of Herrick,[1] Bean,[2] White et al.[3] and Mintz and Katz[4] as well as many others the clinical picture and prognosis for infarction has evolved from long and thorough study of *clinically* recognized cases. Since it was recognized early in this series that 20 per cent of myocardial infarctions seen at the autopsy table were not clinically or electrocardiographically recognized, we believe that this type of "reverse" approach from a postmortem series will give a more accurate and unbiased viewpoint. This first study is primarily a statistical evaluation of the basic material.

MATERIAL

Six hundred seventy-nine hearts with myocardial infarctions found in routine postmortem examinations made at the Los Angeles County Hospital between June, 1942, and April, 1946, were reviewed. Statistical evaluation of the roles of age, sex, hypertension, diabetes, race and causes of death was possible. Table 1 presents the autopsy population from which the 679 myocardial infarctions were drawn. Of the 5,076 autopsies performed within the age range of the infarction group (twenty to ninety-five years), 61.5 per cent were men and 38.5 per cent women. Negroes comprised 494 or 8.3 per cent of the whole. The average age of death among those over fifty years of age (94 per cent of the infarction deaths occurred in this group) was 67.8 years. These simple facts about the "population" from which these infarctions were culled give a more secure basis for

TABLE 1
FREQUENCY TABLE FOR ALL NECROPSIES PERFORMED DURING PERIOD OF STUDY, JUNE, 1942, THROUGH DECEMBER, 1945*

Age (yr.)	No. Deaths	Unit Age	Unit Dev.†	Unit Sq. Dev.
20–29	203	−3	−609	1827
30–39	442	−2	−884	1768
40–49	681	−1	−681	681
50–59	960	0	0	0
60–69	1225	1	1225	1225
70–79	1138	2	2276	4552
80–89	403	3	1209	3627
90–99	24	4	96	384
Totals	5076	..	2632	14064
Totals (over 50)	3750	..	4806	9788

Mean age of death: 60.2 ± 0.22 yr.
Mean age of death over 50 yr. of age: 67.8 ± 0.16 yr.
Male: Female ratio was 3682:2261, or 1.63 to 1.
Negro necropsies (494) comprised 8.3% of the total.
* Only years within range of infarction group included.
† Deviation.

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interpretation of the findings in the infarction group.

RESULTS

Age. Table II gives the age-sex frequency for the 679 cases of infarction studied. Table III gives the frequency for those dying with recent infarctions. Referring to the Metropolitan Life Insurance statistics for 1944[5] the average life expectancy for those reaching their forty-fifth year was 74.5 years for women and 71.18 years for men. As may be seen from Table II the accident of infarction shortens the life expectancy of women 5.6 years and of men 3.84 years. Extensive reviews of the age factor have been made by White et al.[3] in 1943, Levine and Hindle[6] in 1945 and Mintz and Katz[4] in 1947. The first two authors found the average age of death to be 65.8 and 66 years, respectively. This is in close agreement with our own figure of 67.8 years. The latter workers, however, found an average age of death among their 125 cases of 61.5 years. This group should be compared with those comprising Table III in which it will be noted that the difference between the average ages of death of the sexes is 3.3 years in favor of the women (66.3 years for men, 69.0 years for women). Mintz and Katz[4] had a 3.8 year difference of the same order even though their overall average age of death was 5.8 years less than the group presented in Table III. As we have no way of knowing the average age of death for all patients coming to autopsy at their institution, we can only surmise it is also below that found in this study (60.2 years, Table I).

TABLE II
AGE-SEX FREQUENCY—TOTAL INFARCTION SERIES

Age (yr.)	No. Deaths		Unit Age	Unit Dev.		Unit Sq. Dev.	
	M*	F*		M	F	M	F
20–24	1	0	−9	−9	0	81	0
25–29	0	1	−8	0	−8	0	64
30–34	2	1	−7	−14	−7	98	49
35–39	6	1	−6	−36	−6	216	36
40–44	11	1	−5	−55	−5	275	25
45–49	12	6	−4	−48	−24	192	96
50–54	29	10	−3	−87	−30	261	90
55–59	45	15	−2	−90	−30	180	60
60–64	59	29	−1	−59	−29	59	29
65–69	84	43	0	0	0	0	0
70–74	89	53	1	89	53	89	53
75–79	82	37	2	164	74	328	148
80–84	31	17	3	93	51	279	153
85–89	8	4	4	32	16	128	64
90–94	1	1	5	5	5	25	25
Totals	460	219	..	−15	60	2211	892

Mean age of death (total group): 67.8 ± 0.41 years.
Mean age of death (males): 67.34 ± 0.51 years.
Mean age of death (females): 68.90 ± 0.69 years.
* M represents males; F represents females.

TABLE III
AGE-SEX FREQUENCY—RECENT INFARCTION DEATHS

Age (yr.)	No. Deaths		Unit Age	Unit Dev.		Unit Sq. Dev.	
	M	F		M	F	M	F
20–24	1	0	−9	−9	0	81	0
25–29	0	0	−8	0	0	0	0
30–34	1	0	−7	−7	0	49	0
35–39	3	0	−6	−18	0	108	0
40–44	9	1	−5	−45	−5	225	25
45–49	9	5	−4	−36	−20	144	80
50–54	18	6	−3	−54	−18	162	54
55–59	30	11	−2	−60	−22	120	44
60–64	37	21	−1	−37	−21	37	21
65–69	54	35	0	0	0	0	0
70–74	43	39	1	43	39	43	39
75–79	44	31	2	88	62	176	124
80–84	16	10	3	48	30	144	90
85–89	5	1	4	20	4	80	16
Totals	270	160	..	−67	49	1369	493

Mean age of death (total group): 67.3 ± 0.50 years.
Mean age of death (males): 66.3 ± 0.68 years.
Mean age of death (females): 69.0 ± 0.68 years.

Sex. Table II shows 67.8 per cent were men and 32.2 per cent were women. The ratio is only 2.1 to 1. Hedley,[7] Rathe[8] and Mintz and Katz[4] found similar results. The bulk of previous reports from that of Parkinson and Bedford[9] in 1928 to that of Clawson[10] in 1941 emphasized ratios ranging from 7:1 to 4:1 males to females. Even the 2:1 ratio found in this series superficially indicates a predilection for men. Let us look at the "population" of deaths from which they were drawn. It is easily seen from

Table I that 61.5 per cent of all deaths were males, 38.5 per cent being females. Comparing the ratios of the infarction group with the general mortality series, the difference between the two proportions (6.3 per cent) is but little greater than the standard error of difference between the two proportions (5.7 per cent),—making the variation certainly only a chance possibility. Unfortunately, the previous workers who have remarked upon the relatively small sex difference have not considered this aspect in interpretation of their findings.

Having demonstrated the impartiality of nature with respect to the sex of the victims of infarction, it remains to be seen if the picture of the disease, once acquired, is altered by the sex of the victim. In Table III deaths were associated with recent infarction. Here the average age of death was 69 years for women, 66.3 years for men. In contrast with the age difference between men and women in the total series, this 2.7 year difference is of statistical significance. It will also be noted that comparison of the average span for men shortened one year and lengthened 0.1 year for women when infarction is an immediate factor in the cause of death. Since the segregation of deaths associated with recent infarction altered the average age of death among men ten times that obtained for women, the results indicate that men either die of their infarctions at an earlier age, or that deaths with recent infarction make up a sufficient per cent of the total number of infarctions among women to leave the average age of death almost unaltered.

Checking Tables II and III one finds 73.1 per cent of all women with infarctions died with a recent infarction but only 58.7 per cent of the men so died. This difference is of important statistical significance. First, it shows that women are stricken more seriously than men and, in conjunction with the age differences, at a later time in life. Secondly, it demonstrates that a large proportion of men will recover from their attacks to die later of other conditions. This makes the average ages of death for men and women in the total series (Table II) insignificantly different as compared to the significant difference among those dying of recent infarctions alone. (Table III.)

Table IV attacks the assumption of increased susceptibility among women from another angle, namely, the incidence of rupture of the myocardium. While too small a group to render sex comparisons on a statistical basis it is remarkable that the male-female ratio is reversed (22 women to 12 men). This accident accounted for 5 per cent of the deaths in the series and will be considered in more detail later. It does add weight to the assumption that the female heart is unable to withstand infarction as well as the male.

TABLE IV
INCIDENCE OF MYOCARDIAL RUPTURE (DIRECT DATA)

Age (yr.)	Men Dev. from Mean (yr.)	Dev. Sq.	Women		
			Age	Dev.	Sq. Dev.
54	−18.8	353.4	59	−10.7	114.5
			60	− 9.7	94.0
66	− 6.8	46.24	61	− 8.7	75.8
			63	− 6.7	44.9
67	− 5.8	33.64	65	− 4.7	22.2
			66	− 3.7	13.7
70	− 2.8	7.84	66	− 3.7	13.7
			67	− 2.7	7.29
72	− 0.8	0.64	67	− 2.7	7.29
			67	− 2.7	7.29
74	1.2	1.44	70	0.3	0.09
			70	0.3	0.09
76	3.2	10.24	71	1.3	1.69
			72	2.3	5.3
77	4.2	17.64	72	2.3	5.3
			73	3.3	10.9
77	4.2	17.64	75	5.3	28.2
			75	5.3	28.2
75	2.2	4.84	77	7.3	54.8
			78	8.3	69.0
82	9.2	84.64	78	8.3	69.0
			82	12.3	154
84	11.2	125.40			
Totals: 874	0.4	703.6	1534	0.6	827.24

Mean age of death (total ruptures): 70.8 ± 1.15 years.
Mean age of death (males): 72.8 years.
Mean age of death (females): 69.7 years.

The final evidence for the increased danger of this accident to women lies in a

review of the group found to have only a single infarct. Of the total (351) 228 were men and 123 were women. This was fatal to 71.5 per cent of the women (88) and to 44.3 per cent (101) of the men. This difference is well beyond the range of chance based on 2.5 times the standard error of the difference, and conclusively shows that the female heart is less able to recover from infarction.

Race. The influence of race is briefly considered by a comparison between the negro and non-negro sufferers. Of the 679 infarctions found in this survey twenty-three (3.48) were classified as negro. Thirteen were women; ten were men. As 8.3 per cent of all autopsies during this period were performed on negroes, there was a 4.9 decline in the incidence of infarction. The standard error of the difference between the two proportions is 0.78 per cent. As the outer limits of expected chance correlation is 2.5 to 3 times the standard error, it is seen that the apparent resistance of the negro to this accident is highly significant. Wartman and Hellerstein[11] in a recent review also found the number of negroes afflicted with myocardial infarction to be less than the race incidence would lead one to expect. They also found, as reported here, that it was more frequent in negro women than in white women. However, as in all statistical work, close check must be kept on the variables involved. Certain factors still unknown to us may lessen the value of the above results. Not considered here is the effect of the economic and sanitary environment of the negro as opposed to the white. Certainly poverty, overcrowding, lack of sanitation and physically dangerous fields of employment all tend to terminate life before the victim has reached the "age of infarction."

Hypertension. The factor of hypertension was followed for those dying during 1943 through 1945. Of a total of 240 men and 106 women dying with old or recent infarctions, 142 men (59 per cent) and 69 women (65 per cent) had recorded diastolic pressures over 95 mm. of mercury. This 6 per cent increase in female hypertensives is scarcely greater than the standard error of the proportion (5 per cent) when the two sexes are statistically compared, again showing no sex difference in this aspect of the problem of myocardial infarction. These results show 61 per cent of this infarction group had hypertension. This is considerably above the 49 per cent reported by Parkinson and Bedford[12] in 1928, and greatly exceeds the 35.9 per cent reported in 1947 by Mintz and Katz. The latter authors consider their criteria of 90 mm. diastolic pressure and neglect of systolic rise as accounting in large measure for their results. The 61 per cent found in our group, however, had almost identical criteria, varying only in requiring a diastolic pressure of 95 mm. of mercury.

Mintz and Katz[4] also found hypertension occurring more frequently among women than men (49.4 per cent as opposed to 29.7 per cent). From their tables it can be calculated that this 19.7 difference is between 2.5 and 3 times the standard error of the difference between their two proportions. In statistical evaluation this is beyond the expected chance occurrence by only a narrow margin. The fact that our series falls within the bounds of chance may depend on the difference in method of sampling in the two studies. Even as it has been shown that other aspects of infarction are altered when *all* victims are considered, so may the clinical impression with respect to the hypertensive factor be somewhat distorted. It is not meant to be inferred that hypertension has any etiologic relationship with myocardial infarction, particularly since about 40 per cent of people over forty have some degree of systolic and diastolic hypertension.

Diabetes Mellitus. Table v gives the age-sex frequency among the sixty-six diabetics found in this study. Of the total, forty-four fell within the group studied for evidence of hypertension. Of the forty-four, only nineteen were found to have hypertension (six men and thirteen women). Although this constitutes 43 per cent of the diabetic group as compared to 61 per cent of the total, the size of the series creates so large

a standard error (7.9 per cent) that no conclusions may be drawn.

With respect to certain other features of infarction among diabetics we can stand on firmer statistical ground. The average age of death among the diabetic group is

TABLE V
AGE-SEX FREQUENCY—DIABETIC SERIES

Age (yr.)	No. Deaths		Unit Age	Unit Dev.		Unit Sq. Dev.	
	M	F		M	F	M	F
20–24	1	0	−8	−8	0	64	0
25–29	0	0	−7	0	0	0	0
30–34	0	1	−6	0	−6	0	36
35–39	0	0	−5	0	0	0	0
40–44	0	0	−4	0	0	0	0
45–49	0	0	−3	0	0	0	0
50–54	3	4	−2	−6	−8	12	16
55–59	2	5	−1	−2	−5	2	5
60–64	7	11	0	0	0	0	0
65–69	6	6	1	6	6	6	6
70–74	5	10	2	10	20	20	40
75–79	3	1	3	9	3	27	9
80–84	1	0	4	4	0	16	0
Totals	28	38	..	13	10	147	112

Mean age of death (all diabetic patients): 64.2 ± 1.17 years.
Mean age of death (male diabetics): 64.8 years.
Mean age of death (female diabetics): 63.8 years.
* All three mean values are within the standard error for the group mean.

64.2 years, or 3.6 years younger than that for the general series. This is approximately three times the standard error of the difference between the two means (1.2 years); hence it is a significant decrease in the expected life span. Next the complete reversal of the male-female ratio (22 males to 28 females) sets the diabetic apart from his fellow sufferers. Both these findings have been found true in past studies.[4] It has often been assumed that this unfavorable prognosis of myocardial infarction among diabetics is due to the increased severity of atherosclerotic changes in diabetics. While this study is unable to answer this question directly, a consideration of Tables VI and VII will suggest a remarkable conclusion. These tables in presenting the causes of death in the general and diabetic groups have been separated into those surviving over four months and those dying in less than that time. This rough segregation was

TABLE VI
PRIMARY CAUSES OF DEATH IN THE GENERAL SERIES

Primary Cause	Survival over 4 Mo.		Survival under 4 Mo.	
	Male	Female	Male	Female
Infarct, cardiac	99	40	76	69
Infarct, plus pulmonary embolism	11	5	10	5
Infarct, plus cerebrovascular accident	15	6	9	13
Infarct, plus vascular accident	6	3	3	3
Infarct, plus miscellaneous conditions	19	9	22	7
Congestive failure	57	17	2	0
Pneumonia	19	4	2	0
Cerebrovascular accident	30	12	1	0
Pulmonary embolism	15	9	0	1
Vascular accident	13	5	0	0
Miscellaneous	49	11	2	0
Total	333	121	127	98

TABLE VII
PRIMARY CAUSES OF DEATH IN THE DIABETIC SERIES

Primary Cause	Survival over 4 Mo.		Survival under 4 Mo.	
	Male	Female	Male	Female
Infarct, cardiac	10	11	7	13
Infarct, plus pulmonary embolism	0	0	2	0
Infarct, plus cerebrovascular accident	0	2	0	1
Infarct, plus vascular accident	0	0	0	0
Infarct, plus miscellaneous conditions	0	1	2	0
Congestive failure	2	1	0	0
Pneumonia	2	3	0	0
Cerebrovascular accident	0	2	0	0
Pulmonary embolism	1	1	0	0
Vascular accident	0	0	0	0
Miscellaneous events	2	3	0	0
Total	17	24	11	14

necessitated by inadequate evidence of the time of occurrence of an infarction episode revealed at necropsy by an old area of myomalacia. In the general group 66.9 per cent survived over four months. In the diabetic group 64 per cent survived over four months. This difference is less than the standard error of the two proportions itself, 7 per cent. From this it is seen that diabetes *per se* should not influence the prognosis if the acute episode is survived. On the other hand there is a 22.3 per cent increase in the percentage of diabetics dying primarily from myocardial infarction. This is greater than three times the standard error. Hence the immediate prognosis of the acute attack in a diabetic is much more serious than in the non-diabetic. Again it is to be noted that of the sixty-six diabetics, fifty-one, or 77 per cent died with a recent infarct. In the total series this group constituted 63 per cent. The 14 per cent increase is beyond the statistically significant bounds of chance. The difference may, therefore, be attributed to the diabetic state. The total number of single infarctions among the diabetics constitute 60.6 per cent as opposed to 51.7 per cent in the general series. This is within the bounds of statistical chance association and is of no significance.

If it is assumed that the atheromatous changes incident to the diabetic state deplete the myocardial reserve to a degree that will account for the lessened life expectancy, significantly fewer diabetics should survive the initial attack and a greater number of single infarcts should be found among diabetic hearts at necropsy. This study supports neither of these contentions. On the other hand it does show that many more diabetics die primarily of their myocardial infarctions whether on the first attack or on succeeding attacks. These findings point to the difficulty in control of the diabetic state itself and not to structural arterial alterations as the primary factor in shortening the life expectancy of these people.

Rupture of the Myocardium. As previously noted rupture of the heart occurred in thirty-four instances. Thus this accident occurred as a cause of death in 5 per cent of the total series. In 1928 Parkinson and Bedford[9] found 6 per cent of their necropsy series had rupture of the myocardium. In 1938 Bean[2] reviewed 300 cases of infarction and found 6 per cent with rupture. In 1948 Diaz-Rivera and Miller[12] found five ruptures among 147 hearts with myocardial infarction. Further consideration of these cases reveals a marked variance from the general infarction group. Table IV indicates that not only is the male-female ratio reversed, but the average age (70.8 years) is significantly older than the average for the general series (67.8 years). Finally the average age of death for men dying of rupture was 72.8 years, while that for women was 69.7 years, a direct reversal of the expected course of events in myocardial infarction. It is also of interest that twenty-nine of the thirty-four had no evidence of a previous infarction. The frequency of initial infarction among ruptured hearts, the female preponderance, and the tendency for it to occur in a much older male age group all point toward special qualifications for this accident. A common denominator to the above observations could be expressed as inadequate collateral circulation. In many of these cases there was minimal evidence of previous myocardial fibrosis or even areas of tiny scarring. This might imply rupture is associated frequently with an accidental occlusion superimposed on a vascular system unprepared for adequate collateral circulation by the atherosclerotic changes gradually acquired by most hearts subjected to infarction.

Thromboembolism. A number of studies of the incidence of pulmonary embolism and thromboembolic phenomena have appeared. In Table VIII a representative group over the past twenty years is summarized. The average incidence for this group of studies closely coincides with the findings in the present series.

It is of interest that pulmonary embolism contributed to the cause of death in 8.25 per cent of this series. Among those dying

primarily of their infarction it occurred in 7.2 per cent of the observed cases. An estimate of the incidence of all thromboembolic accidents in this series can be made by summation of the pulmonary emboli, vascular accidents (excepting seven rup-

TABLE VIII
INCIDENCE OF PULMONARY EMBOLISM
(PAST TWO DECADES)

Author	Infarcts Reviewed	Pulmonary Emboli	
		No.	Per Cent
(1928) Parkinson and Bedford[9]	83	8	(10)
(1930) Conner and Holt[13]	287	21	(7)
(1937) Blumer[14]	175	16	(9)
(1938) Bean[2]	300	21	(7)
(1941) Woods and Barnes[15]	128	13	(10)
(1945) Nay and Barnes[16]	100	14	(14)
(1947) Hellerstein and Martin[17]	160	8	(5)
(1948) Present series	679	56	(8)
Total	1,812	157	(8.7)

tured aortic aneurysms), and cerebrovascular accidents contributing to the immediate cause of death, excepting those not closely associated with the myocardial accident. This amounts to 126 cases or 18.5 per cent of the total group. Of the 430 recent infarctions 21 per cent had thromboembolic accidents. This facet of the problem of infarction has received thorough review by Hellerstein and Martin[17] and Katz and Mintz.[18] The former found thromboembolic lesions contributing to the cause of death in 27 per cent of 169 autopsies showing myocardial infarction. The latter analyzed 572 cases (clinical) and found fifty-two embolic episodes.

SUMMARY AND CONCLUSIONS

1. Among 679 necropsies showing old or recent myocardial infarction the average age of death was 67.8 years. The sex differences with respect to both incidence and age of death were insignificantly altered from the corresponding ratios among the 5,943 deaths occurring during approximately the same period.

2. Women are more likely to suffer a fatal outcome from the infarct than men, as demonstrated by the increased mortality with single infarcts and the increase in instances of rupture of the heart in women.

3. Hypertension did not show the significant predilection for the female sufferer observed by other workers.

4. The 3.4 per cent of this study made up of the negro race shows a distinctly lowered incidence among this group. The significance cannot be evaluated at this time.

5. Diabetics differed from the general group by showing a greater incidence of infarction in women, and by showing a decreased life expectancy of 3.6 years. Evidence is also presented that the control of the diabetic during the acute episode, and not the vascular status of the patient, is the primary cause for the more serious prognosis in these individuals.

6. The causes of death in the study are tabulated and two of particular interest (myocardial rupture, thromboembolism) discussed.

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Myocardial Infarction*

II. A Re-evaluation of the Diagnostic Accuracy of the Electrocardiogram

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THE following presentation is aimed at evaluation of the electrocardiogram as a diagnostic aid in myocardial infarction. For this study we have used the autopsy material presented in Part I of this communication as the principal source of autopsy-proven myocardial infarctions, and to this large group we have added an additional small series, again of autopsy-proven myocardial infarctions, in an effort to evaluate the importance of precordial electrocardiography. The early work of Pardee[1] and the recent extensive studies of Katz have been supplemented by numerous investigators in the intervening years. For comparative purposes we are presenting a review of results in the following tables: Table I represents the accuracy of established electrocardiographic patterns in the recognition of myocardial infarction as seen when clinically recognized cases are traced to the autopsy table. Table II presents EKG pattern accuracy as found incidental to a review of autopsy material.

TABLE I

Author	Cases Followed to Necropsy	Per Cent with Infarction Pattern
Feil et al., 1938	34	82
Rosenbaum and Levine, 1941	68	82
Master et al., 1944	65	72

TABLE II

Author	Necropsies with EKG Records	Electrocardiograms with Infarction Patterns
Applebaum et al.	36	27
Barnes, A.	21	19
Sprague et al.	61	26
Saphir et al.	12	10

The second table shows only 63 per cent of the electrocardiograms gave evidence of infarction. The incidence is this high only due to the bias of inclusion of the statistically questionable, small series reported by Barnes and Saphir. Among the 306 infarcted hearts with adequate premortem studies, over 20 per cent were unrecognized by any clinical means. This not only explains the difference in results shown in Tables I and II, but also shows that review of unselected consecutive autopsies is the only true appraisal of the electrocardiographic diagnostic crutch.

METHOD

Two separate series of autopsy-proven myocardial infarctions were compared. Over a five-year period 740 autopsy protocols of myocardial infarction were found. Three hundred six proved satisfactory for electrocardiographic evaluation. To do this the EKG had to be taken within twenty-four hours to two weeks after the infarction occurred. Three standard leads with a single CF_4 chest lead constituted 256 of the cases satisfying our criteria. The second series

* From the Post-graduate Division of the University of Southern California, Department of Cardiology, Los Angeles, Calif. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

was a group of fifty cases with six chest leads, three unipolar limb leads in addition to the three standard limb leads.

All tracings were reread with complete knowledge of the existence of infarction. This was done to analyze the factors most likely to prevent correct interpretation. The material was also prepared statistically to evaluate the accuracy of both recognition and localization of infarctions.

TABLE III
PATTERNS PREVENTING DIAGNOSIS

	Original Reading	Review by R. S. C.
Bundle branch block	32	20
Left ventricular strain	18	15
Abnormal T waves	..	13
Ventricular tachycardia	3	3
Abnormal non-specific changes	..	12
Digitalis effect	32	1
Normal EKG	7	3

RESULTS

Two Hundred Fifty-six Cases with Three Standard Leads and CF_4. In this group clinical history and physical examination alone suggested the diagnosis in 76.5 per cent of the instances. Only 51.5 per cent of the EKG interpretations suggested the presence of infarction. With full knowledge that the tracing was taken at the time of an infarction our subsequent review still failed to show evidence of infarction in 33 per cent. By limiting himself to a single chest lead in addition to the standard limb leads the electrocardiographer cannot match purely clinical methods of diagnosis. Even more unfortunate is the unreliability of this type of electrocardiogram in ruling out the presence of infarction in clinically questionable cases.

Table III presents a rough classification of the findings in the "silent" tracings. In both the original reading and our subsequent analysis bundle branch block was the most common pattern making the electrocardiographic diagnosis of infarction impossible. Equally common in the eyes of the original readers were patterns suggesting digitalis effect. Dr. L. N. Katz[10] has aptly compared the electrocardiographic manifestations of digitalis to the classical clinical pleomorphism attributed to syphilis. The electrocardiographer should have exact knowledge of the story behind the tracing before ascribing to digitalis any effects beyond the most characteristic pattern alterations. The most heartening finding, however, was the extreme infrequency of a truly normal electrocardiogram in the presence of myocardial infarction.

The second desire of the clinician in requesting an EKG is to localize the infarct. This was attempted by the original readers in only 111 of the 132 suggestive tracings. Localization was correct in 100 instances. The accuracy of the three standard lead electrocardiogram with only a single CF_4 chest lead is then 76 per cent if an infarction pattern is recognized.

Fifty Cases with Six Precordial Leads in Addition to Three Standard Limb Leads and Unipolar Limb Leads. Clinical recognition without the benefit of an electrocardiographic "crutch" maintained an acuity of 70 per cent, not unlike that found in the preceding series. However, where the previous group offered but 51.5 per cent electrocardiographic recognition, the use of multiple chest leads increased diagnostic accuracy to 80 per cent. This 28.5 per cent increase in diagnostic ability is far beyond the chance expectations of the two groups.

Although too small for statistical evaluation, the 20 per cent failing to give evidence of infarction showed the same masking patterns previously noted. Four were bundle branch blocks; three were interpreted as left ventricular strain; two were considered to be digitalis effect; and one was recorded only as diffuse cardiac disease.

The total per cent of infarctions recognized when both history and multiple chest lead electrocardiograms were studied constituted 90 per cent of the fifty cases reviewed. This is a far happier outlook than

that of the earlier series which left over 20 per cent of the patients unrecognized.

CONCLUSIONS

1. A single precordial lead in addition to the three standard leads offered patterns suggestive of myocardial infarction in only 51.5 per cent of 256 cases reviewed from necropsy material.

2. History combined with physical examination alone offered evidence of infarction in 70 to 76 per cent of all cases reviewed.

3. Multiple precordial leads in addition to three standard leads gave evidence of infarction in eighty per cent of fifty necropsy cases reviewed.

4. Localization of the 111 infarcts suggesting diagnosis on EKG with a single precordial lead was accurate in 76 per cent of the instances.

5. Localization in forty cases suggestive of infarction when multiple precordial lead technic was used showed 92.5 per cent accuracy.

6. The three main factors responsible for interfering with the diagnosis of infarction were the presence of bundle branch block, left ventricular strain or digitalis effect.

7. Of all the cases with infarction, in less than 3 per cent of the first series and in none of the second series was a normal electrocardiogram present. Hence repeated electrocardiograms with a normal pattern in the presence of suspected infarction represent strong evidence that no infarction has occurred.

8. The limitations of three standard leads augmented by only a single CF_4 precordial lead are sufficiently great that multiple precordial lead technics should become routine office and hospital procedure whenever the question of myocardial infarction arises.

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Cor Biloculare*

Report of Four Cases

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THE advent of the newer types of surgical procedures devised for the correction of certain varieties of congenital heart abnormalities has made it increasingly important to attempt to arrive at an accurate clinical diagnosis in each case. Cor biloculare has a largely negative significance because it should be ruled out in most instances in which surgery is under consideration. The closure of a persistent ductus arteriosus or the formation of an arteriovenous shunt would be of little avail in a heart in which there was already a complete intermingling of systemic and pulmonary blood. However, in the event of atresia or stenosis of either the aorta or pulmonary arteries the establishment of an additional shunt between these vessels might be beneficial to the circulation. Cor biloculare is usually incompatible with a life longer than a few days and the chance of occurrence in any patient of more advanced age is small; however, enough have survived for from several to many years to warrant a consideration of this anomaly when the differentiation of congenital heart disease is involved.

A study of the literature and examination of the specimens of cor biloculare and other types of congenital heart lesions in our own pathology departments revealed that the term cor biloculare did not define a precise anatomic and pathologic entity but that it applied to a group of congenitally deformed hearts which most nearly approached, structurally and functionally, a true two-chambered organ. Each case had its own variations, and there was a gradation from the purely biloculate through the triloculate to the normal four-chambered heart, with a specimen for almost any given stage of arrested development.

The four cases herein reported are those with hearts that conformed to the structural pattern of cor biloculare, with the exclusion of cor triloculare biventriculosum and others that actually functioned as two-chambered hearts.

CASE REPORTS

CASE I. Baby C., a male infant weighing 7 pounds 12 ounces, was born to healthy parents after a normal period of gestation by spontaneous delivery under open ether anesthesia. He appeared in good condition at birth. There was no family history of congenital defects. The newborn suddenly became cyanotic and dyspneic twenty-four hours after delivery and at this time a physical examination was done. The infant was found somewhat dehydrated and had a temperature of 102°F., with a pulse of 150 and respirations of 30 per minute. The chest was normal to inspection, the apex beat was located 3.5 cm. to the right of the mid-sternal line in the fifth interspace, while the area of cardiac dullness was 3 cm. to the right in the fifth interspace and 1.5 cm. to the left of the mid-sternal line in the fourth interspace. A to-and-fro murmur which later disappeared was heard over the base at the onset of the cyanosis. The lungs were clear, the liver at the costal margin and there was no dependent edema. A roentgenogram of the chest showed the presence of a small thymic shadow and a large cardiac shadow with the apex pointing to the right. There was no indication of a transposition of the abdominal viscera. An electrocardiogram (Fig. 1) showed sinus tachycardia with myocardial damage. The

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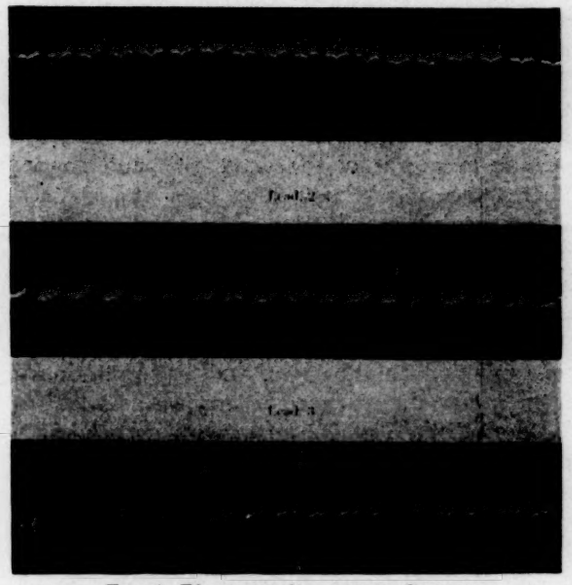

FIG. 1. Electrocardiogram in Case I.

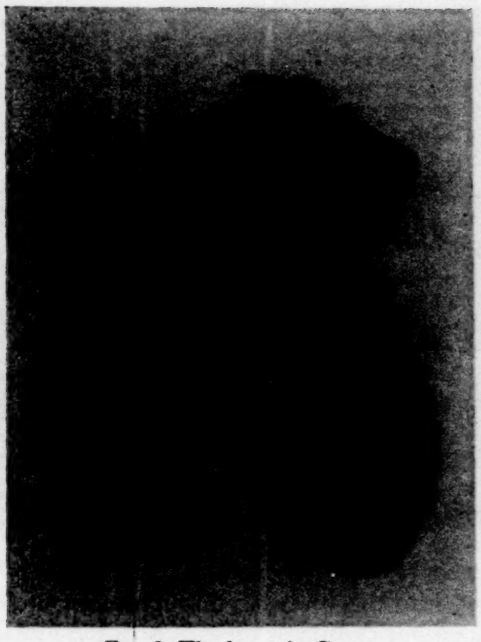

FIG. 2. The heart in Case I.

baby was given oxygen but failed to respond and expired on the fourth dav of life.

Examination of the thorax at autopsy revealed the heart located largely to the right of the midline, with the apex in the right midclavicular line. The aorta originated to the right of and anterior to the pulmonary artery, and except for this transposition these vessels were not remarkable.

The heart (Fig. 2) was essentially a two-chambered organ. The right and left atrial appendages were well formed but the lack of an interauricular septum other than a narrow ridge caused the chambers to function as a common auricle. The openings of the venae cavae and the pulmonary veins were all situated on the right side of the interauricular line of demarcation. The mitral valve connected the auricle with a greatly dilated and hypertrophied right ventricle. The pulmonary artery originated from the base of this ventricle to the right of the tricuspid valve and extended directly upward behind the aorta. Communicating with the right ventricle, and situated to the right of the pulmonary valve was a very rudimentary right ventricle which existed only as a narrow and shallow slit in the muscle of the anterior right ventricular wall. The aorta originated from the upper angle of this minute cavity and passed upward and anterior to the pulmonary artery. The abdominal viscera showed no situs inversus or other anomalies, nor was the remainder of the body pathologically remarkable. The anatomic diagnosis was congenital heart composed of a common auricle and a single functioning ventricle, with transposition of all the chambers of the heart.

CASE II. Baby G. was a white female, 5 pounds, 10 ounce infant born after an uneventful pregnancy. The baby was delivered under ether anesthesia as a footling breech without any difficulty. The respirations started spontaneously, but shortly after birth the child developed cyanosis which was unaffected by treatment with oxygen and the usual respiratory stimulants. A diagnosis of congenital heart disease, type undetermined, was made. The physical examination was entirely negative except for the findings of marked cyanosis and dyspnea, which steadily increased until the child died three days after delivery.

At autopsy there was livid discoloration of the skin. When the thorax was opened, an anomaly of the great vessels was immediately apparent; therefore the heart and lungs were removed *in toto* for inspection. The heart was composed of two compartments, an approximately normal sized right auricle and a common ventricle which was larger than a normal right and left ventricle combined, and rather conical in shape with an extremely broad base. The left auricle was absent except for a small tag of non-functional atrial tissue situated at the base of the ventricular mass. The superior and inferior venae cavae together with the right and left pulmonary veins entered the auricle, which

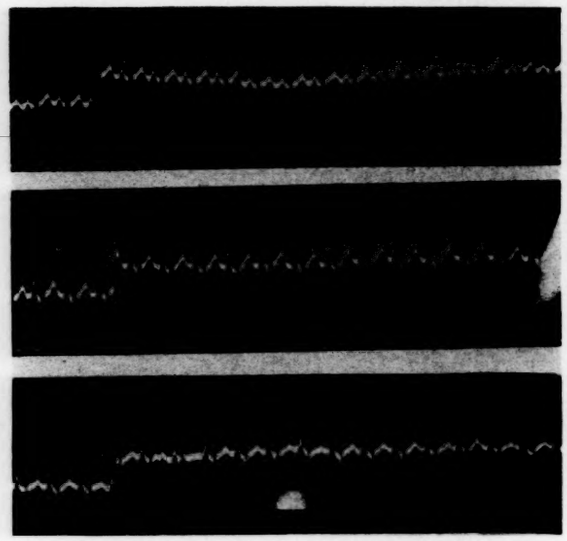

FIG. 3. Electrocardiogram in Case IV.

opened into the ventricle through a valve composed of four distinct leaflets. Extending upward from the base of the heart in a position usually occupied by the pulmonary artery was a large, anteriorly placed arterial trunk. At the exit from the ventricle was a normal valve consisting of three cusps. It was difficult to identify this vessel as either the aorta or the pulmonary artery, but it probably represented the latter because just to the right was discovered a small fibrous cord which was evidently an atretic aorta. The large common vessel passed cephalad for a distance of 8 mm. at which level it gave origin to the right and left pulmonary arteries which continued to the lungs in the normal manner. Above this point the trunk narrowed slightly to form an aorta from which coursed the usual branches.

The remainder of the body organs were normal. The anatomic diagnosis was congenital abnormality of the heart manifested by a single auricle separated by a quadricuspid valve from a single ventricle, and a single arterial trunk common to the pulmonary and general circulations.

CASE III. Baby K., a male infant, was born by a spontaneous delivery after a normal prenatal course. The mother's first and only other child was normal in every respect. The newborn established respiration shortly after delivery and no abnormal findings were noted at the physical examination. The baby was apparently in good condition until thirty-eight hours after birth when cyanosis and considerable respiratory difficulty were noted. The cyanosis and dyspnea increased rapidly in spite of treatment with stimulants and oxygen, and death occurred approximately forty-two hours after birth. No clinical diagnosis was made.

When the thorax was opened at autopsy both lungs were found to be well expanded and the cardiac area was of the usual size and shape. There were a few petechiae over the thymus which was normal in size for a newborn. One great vessel originated from the heart in the position normally occupied by the pulmonary artery. Just above the heart this large vessel gave off direct branches to the lungs which corresponded to the right and left pulmonary arteries and then formed a structure similar to the normal arch of the aorta with its branches, and continued downward to form the thoracic aorta. The heart consisted of a single auricle and ventricle, separated by a tricuspid valve. The single ventricle communicated with the single arterial trunk through a valve having three cusps. The single auricle received the venae cavae and the pulmonary veins. The remainder of the body, including the abdominal viscera, was normal. The anatomic diagnosis was a congenital heart consisting of a single auricle and a single ventricle with a single arterial trunk.

CASE IV. D. V., a three year old boy, was admitted to the hospital with the signs and symptoms of congestive cardiac failure. The records obtained from the hospital where the child was born indicated that it was delivered spontaneously at term. A chest plate taken three days after birth revealed the heart to be shifted to the right and of normal size. The parents disclosed that the child had become cyanotic shortly after birth. The patient was maintained on digitalis therapy the greater part of his life and in spite of this he suffered intermittent episodes of dyspnea, pedal edema and cyanosis, the latter being more severe when he cried. He had occasional attacks of syncope and vomited frequently. He never learned to walk and was able to talk only a little. During the week prior to his hospitalization a marked exacerbation of his symptoms occurred. Physical examination revealed dyspnea, marked cyanosis and edema of the dependent parts. The neck veins were distended. The heart was enlarged to the left and a loud, harsh systolic murmur was heard over the entire precordium, being loudest at the base. No thrills were palpable. The heart rate was too rapid to count accurately. The blood studies showed 20 Gm. of hemoglobin, 6,400,000 erythrocytes, a hematocrit of 72.5, a mean

corpuscular hemoglobin concentration of 28 per cent. The cephalin flocculation test was negative. The electrocardiogram (Fig. 3) showed sinus tachycardia, right axis deviation and myocardial damage. A comparison between these studies and similar ones done at the ages of eleven weeks and twenty-two months revealed no significant differences except that the cephalin test had been positive on occasion. A clinical diagnosis was made of congenital heart disease with hypertrophy, dilatation and interventricular septal defect. The patient was treated with digitalis, mercurial diuretics, oxygen and low fluid intake. He responded temporarily to this therapy but then embarked on a downhill course which ended with his death on the eighth hospital day.

At autopsy the cardiac mass was so great that only the anterior tips of the lungs were visible. The pericardium contained a very small amount of clear fluid. The aorta arose from the anterior portion of the heart in the location normally occupied by the pulmonary artery; the arch and the descending portion were normal. Posterior to the aorta the pulmonary artery could be seen with a normal course and distribution. The auricular portion of the heart consisted of a single chamber: an enlarged right auricle which was demarcated from a very small left auricular appendage by only a narrow band or ridge of muscle tissue. The venae cavae entered the left side of this auricular cavity in approximately normal positions. The auricle communicated with a single ventricle through a dilated tricuspid valve continuous with a fairly well formed mitral structure. There was no sign of an interventricular septum. Under a normal aortic valve there was a small stenotic opening corresponding to the pulmonary valve, through which a probe was passed into an otherwise normal pulmonary artery.

In the abdominal cavity the right lobe of the liver together with the gallbladder was in the left upper quadrant, and the smaller lobe of the liver was in the right upper quadrant. The stomach was situated well under the liver and the small intestine was attached by a long mesentery high over the lumbar spine with the coils placed above the mesentery of the large bowel. There was a complete absence of the spleen and splenic tissues. The head of the cecum and the appendix were located in the left lower quadrant of the abdomen with the descending colon entering the pelvis from the right side. The head was of a size compatible with moderate hydrocephalus, but the cranial cavity was not opened. The anatomic diagnosis was absence of interauricular and interventricular septa, stenosis of the pulmonary valve, and transposition of the liver, the stomach and the intestinal tract, with complete absence of the spleen and moderate hydrocephalus.

COMMENT

The signs and symptoms resulting from cor biloculare were found inconstant and variable. Cyanosis and dyspnea constituted the only findings that occurred consistently in the series of cases reported here. The electrocardiographic and roentgenologic studies were ordinarily of little assistance in establishing the diagnosis and, in addition, associated cardiac defects and anomalies of other organs of the body rendered the clinical diagnosis of this lesion extremely difficult. The most constant physical finding was a systolic murmur heard at all cardiac areas.

Maude Abbott[1] in a comprehensive atlas of congenital heart lesions published in 1936 reported fourteen cases of cor biloculare, nine of which were analyzed with regard to signs, symptoms, associated lesions and other features. This defect was equally common in the two sexes and heredity was of no significance. There were associated anomalies in the heart in all nine cases, with anomalies in the vessels in eight cases and abnormalities elsewhere in two cases. The ductus arteriosus was patent in two, the pulmonary artery was dilated in three, hypoplastic in one and in a dextroposition in seven. Cyanosis was present in eight cases: slight in one, moderate in three and marked in four. Dyspnea occurred in five cases. There were no consistent murmurs or thrills. The longest life span attained by any of these cases which were collected from both American and foreign sources was sixteen years.[2]

Davies and MacConaill[3] reported a case of cor biloculare with hypertrophy of the right auricle. This cardiac lesion was associated with anomalies of the blood vessels. A unique occurrence of cor biloculare in male

identical twins was reported by Giustra and Tosti.[4] The hearts and pathologic findings in the twins were identical. They lived thirty and thirty-nine hours, respectively. The auricular and ventricular septa were completely absent and the right auricle and right ventricle were hypertrophied in both. The two aortas were hypoplastic. Marked cyanosis in one and moderate cyanosis in the other was present during life, with a terminal accentuation in each twin. One had a systolic murmur over the precordium. Sudden cardiac insufficiency was the cause of death in each case.

Lightner[5] had a case of a six month old female infant who had a cor biloculare accompanied by a patent ductus arteriosus and a combination of hypoplasia and dilatation of the aorta. The right auricle and the right ventricle were hypertrophied and there were other anomalies in the heart and elsewhere. Benjamin, Landt and Zeek[6] reported a case of congenital heart disease which was followed for many years. The patient, who was a female, lived to be eighteen years old. She had marked cyanosis and a systolic thrill and murmur over the entire precordium. This case was complicated at first by rheumatic fever and later by subacute bacterial endocarditis. Death was from sudden cardiac insufficiency. The autopsy revealed a heart with complete auricular and ventricular septal defects, dilatation of the right auricle and dilatation of the aorta. A case of cor biloculare with transposition of the great cardiac vessels and atresia of the pulmonary artery was described by Rossman[7] who offered an explanation for this type of malformation on the basis of interruptions in phylogenetic and ontogenetic development. His case was a male who died at the age of nine months and whose cardiac anomalies were associated with somatic abnormalities.

Michelson[8] recorded a case of cor biloculare with persistent truncus arteriosus occurring in a male infant who lived three days. He considered this case peculiar because the cyanosis developed only a short time before death. Shechter and Meranze[9] reported a female infant that was cyanotic from birth until her death twenty-three days later. The heart was found at autopsy to be a cor biloculare. There was also a patient ductus arteriosus and the entire heart was shifted to the right. A congenital heart with one auricle, a large left ventricle and a rudimentary non-functioning right ventricle was reported by Bembenista.[10] His patient exhibited a pronounced cyanosis and lived for seven days. A patent ductus arteriosus was present in addition to the cardiac abnormality.

Cordier, Devos, Gelle and Marcelle[11] reported a case which at autopsy showed a heart with a single auricle, a single ventricle and a single arterial trunk. The authors did not state whether they believed this vessel to be a persistent truncus arteriosus, a persistent aorta or pulmonary artery. There was also a large area of infarction and consolidation in the base of the right lung. Calamari[12] described a case of cor biloculare in a patient with a complete *situs inversus* of the abdominal viscera who lived for thirty days. Ilberg[13] reported a case of cor biloculare in triplets. Junior[14] and Popjak[15] reported cases of cor biloculare, the latter with a solitary arterial trunk from which the pulmonary arteries originated via a persistent ductus arteriosus. This infant became cyanotic five hours after birth and lived for only twenty-one hours. No other abnormalities were present. Rodriguez[16] reported a case of an infant that lived three days and necropsy showed a single ventricle, one ventricular orifice with a single arterial trunk. The ventricle communicated with the right auricle by a single opening. There was only a rudimentary left auricle.

Miskall and Frazer[17] reported a case of cor biloculare with death on the fourth day. There was a quadricuspid valve, mirror image dextrocardia, vestigeal pulmonary artery and transposition of the great vessels. Alexander and White[18] reported another case in which there was a single four-cusped

auriculoventricular valve with an anterior vessel which formed the pulmonary arteries and then went on in the usual course of the aorta and a posterior vessel which branched into the innominate and left common carotid and subclavian arteries.

Case I demonstrates an interesting variation in that the electrocardiogram (Fig. 1) taken shortly before death was atypical for a true mirror-picture dextrocardia. In this electrocardiogram the QRS complexes in Lead I showed a tendency toward inversion and the T waves were definitely inverted. However, instead of the inversion of the P waves, that one would expect to find in a case of mirror-picture dextrocardia, they were actually upright. The suggested explanation for the apparent discrepancy was that in the normal heart the sino-auricular node is placed at the junction of the superior vena cava and the right auricle on the right side, and conversely in mirror-picture dextrocardia on the left side, thus giving rise to an inverted P wave in the electrocardiogram. In Case I there was a transposition of all the chambers of the heart, since the aorta originated from a rudimentary left ventricle to the right of the pulmonary artery, and the vena cavae emptied into that portion of the auricle situated directly behind the aorta into the right side of the common auricle. A dextroversion of the entire heart existed, with a transposition of all the great vessels except the venae cavae which remained on the right side. With this anatomy in mind it was logical to assume that the sino-auricular node remained in the junctional tissue at the point of entrance of the superior vena cava into the auricle, and in this position the node had a normal relation to the heart and the lead wires of the electrocardiograph, which resulted in a tracing with an upright P wave. If this argument is valid, the dextrocardia in this case should not be classified in either of the two groups of true mirror-picture dextrocardial differentiated by Abbott,[1] but somewhere between them as a cor biloculare, mirror-picture dextrocardia, with transposition of the aorta but not of the vena cava.

Case II was classified as a truncus pulmonalis solitarius with aortic atresia, Case III as a persistent truncus arteriosus, both with cor biloculare, while Case IV showed this latter anomaly without the great vessel changes.

In 1942 Rossman[7] stated that thirty-seven hearts with cor biloculare had been reported and these, plus the eight cases reported since 1942 and our own four cases, result in a total of forty-nine cases of this malformation reported to date. Thus the recorded incidence of cor biloculare has more than tripled since Abbott's collection which was published in 1936.

There was a wide range of septal development described in the various reports of cor biloculare and therefore some criteria should be established to classify this condition. In general there are two types: one group includes the hearts with well formed right and left auricles and ventricles but with complete or very nearly complete interauricular and interventricular septal defects; the second group, those in which the right or left auricle or ventricle enlarges to form a common chamber, with the auricle or ventricle of the opposite side present only in rudimentary and non-functioning form.

SUMMARY

Four cases of cor biloculare in various stages of development are reported. One of the cases reported showed dextrocardia; two of the cases had a single arterial trunk and one case had a total absence of spleen or splenic tissue.

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Cor Triloculare*

Report of Four Cases

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THE advances in the surgical treatment of certain types of congenital heart disease necessitates careful study and differential identification in each type of cardiac abnormality. Cor triloculare, like cor biloculare, has a largely negative significance in that it should probably be ruled out when surgical treatment is considered. The surgical formation of an arterial shunt or closure of a persistent ductus arteriosus would not be beneficial and probably would be harmful in the presence of a two- or three-chambered organ. Though most patients with cor triloculare die in infancy, one of those reported herein lived to the age of thirty-five years and others have survived long enough to warrant their consideration in the differential diagnosis of congenital cardiac anomalies.

Only the literature since 1936 was reviewed because Abbott's "Atlas of Congenital Cardiac Disease"[1] published in that year contains a table including presumably all of the cases of cor triloculare reported prior to that date. Abbott found a total incidence of forty-two cases of cor triloculare of which fifteen were cor biventriculare and twenty-seven cor biatriatum. In eighteen of the forty-two cases the trilocular heart was the primary lesion; in the remaining twenty-four cases it was considered as complicating other defects. The eighteen primary cases were analyzed and in this group the maximum age was thirty-five years and the mean age approximately seven years. Cyanosis varying from slight to marked was present in fifteen cases. Eight of the patients presented systolic murmurs but in only one was a thrill felt. The trilocular heart was accompanied by a patent ductus arteriosus in five cases.

Since 1936 reports of fifteen cases of cor triloculare have appeared in the American literature, of which fourteen were biatrial and only one was biventricular. Morgan and Sprenkel[2] reported a case of cor biventriculosum "pseudo-triloculare" in which there was only a rudimentary interatrial septum, the interventricular septum being also defective and the heart further deformed by an anomalous and stenotic mitral valve and a cleft in one of the aortic leaflets. Sprenkel[3] reported a case of cor biatrium "pseudo-triloculare" which had a rudimentary left ventricle and was complicated by atresia of the mitral and aortic valves, hypoplasia of the aorta and the left auricle, patent ductus arteriosus and foramen ovale, and an interventricular septal defect. A heart with two atria and one ventricle occurring in a baby girl who lived only three days and had marked cyanosis was reported by Rukstinat.[4] This heart also showed an aortic stenosis, a patent foramen ovale and a coarctation of the aorta situated 15 mm. from the aortic leaflets. Drey, Strauss and Gray[5] had a case of biatrial cor triloculare with a malposed ventricular septum but normal position of the great vessels which they believed to be a duplicate of the heart reported by Holmes in 1824. The patient was a fourteen year old girl who exhibited marked cyanosis and a loud systolic murmur over the precordium but had no pulmonary or peripheral edema.

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The autopsy revealed a cerebral abscess and renal infarction in addition to the cardiac findings. Taussig[6–10] has described five cases of cor triloculare. All were biatrial and all were complicated by other defects: four had a patent ductus arteriosus, three had pulmonary atresia, two had tricuspid atresia, two had mitral atresia, and in one the great vessels were completely transposed. All of the patients were cyanotic, only two presented murmurs and in only one was a thrill felt. All died in early infancy, the oldest attaining the age of five months. Moskowitz[11] described a trilocular heart with two auricles in which there was also a true dextrocardia with transposition of the great vessels and an interatrial septal defect. A to-and-fro murmur was evident in the patient who died at the age of four months after progressive cyanosis.

In 1944 Clawson[12] analyzed 141 cases of congenital heart disease which were disclosed in 15,597 autopsies performed at the University of Minnesota from 1936 to 1941. Seven of these 141 hearts were triloculare; all were of the biatrial type and all of the patients were markedly cyanotic. They had all died in the first year of life. Glendy, Glendy and White[13] found a cor biatriatum triloculare in a patient who was clinically diagnosed as having rheumatic heart disease with failure. Systolic and diastolic murmurs were heard at the apex. Cyanosis was completely absent. The electrocardiogram showed intraventricular block and right axis deviation. The roentgenographic shadow of the heart was so large in all diameters that a pericardial effusion was suspected but only blood was obtained upon pericardicentesis. In addition to the trilocular heart the autopsy revealed a rudimentary left ventricle, patent foramen ovale, slight coarctation of the aorta and hemopericardium. Dunsky[14] recorded a case of cor triloculare biatriatum complicated by tricuspid atresia, patent foramen ovale, transposition of the arterial trunks, hypoplasia of the aorta, coarctation of the aortic isthmus and patent ductus arteriosus. The patient, the first of twins, had no murmurs or cyanosis and lived five days.

There have been reports of twelve trilocular hearts published outside the United States. Ten of these were biatrial and two were biventricular. Severino[15] reported a heart with complete absence of the interventricular septum. A case of cor triloculare biatriatum with a single arterial trunk and a persistent sinus venosus was described by Diag and De los Reyes.[16] Van Creveld[17] had a case with biauricular heart and associated hydrocephalus. A heart with one ventricle. hypoplasia of the left auricle, agenesis of the mitral valve and aortic atresia was reported by Monserrat.[18] A univentricular three-chambered heart was recorded by Schockaert, Lambillon and Reynaert.[19] A trilocular heart with two atria, tricuspid atresia and corrected transposition of the great vessels was contributed by Sakaki.[20] Rosaria[21] listed a cor triloculare biventriculosum and Luna[22] a cor triloculare biatriatum. Marquez, Basile and Luna[23] described a congenital heart with one auricle, two ventricles and stricture of the mitral valve. In Britain, biatrial trilocular hearts were reported by Walls,[24] and Mehta and Hewlett.[25] A cor triloculare biatriatum with transposition of the arterial trunks was described by Brodie.[26]

The four cases reported here are those in which the hearts conformed to the structural pattern of cor triloculare although they may have functioned as two-chambered hearts.

CASE REPORTS

CASE 1. Mrs. G. J., a thirty-five year old white woman, complained of dyspnea, tiredness, swelling of the abdomen and orthopnea for three months. She stated that she was born with a bad heart, her lips and fingers had always been somewhat purple and that her fingers and toes had always been enlarged at the ends. From early childhood her activity had been restricted but she had never experienced chest pain or swelling of the ankles. She had had frequent headaches and had been bothered by exertional dyspnea for as long as she could remember, but in spite of this had been able to do her housework and had held an eight-hour

per day clerical position until a week prior to her admission to the hospital. She had had the usual childhood diseases but no operations or serious illness. Her menstrual periods had been extremely irregular, varying from two months to a year, and her only pregnancy had terminated in a spontaneous abortion after a gestational period of four months. The family history revealed no evidence of heart disease, tuberculosis or malignancy but two uncles, two aunts and the patient's father had died of diabetes mellitus. Her mother, one sister and two brothers were alive and well.

Examination revealed moderate respiratory distress and some lethargy. She was well developed and slightly obese. Her lips, ears, hands and feet were markedly cyanotic. The distal phalanges of the fingers and the toes exhibited an extreme degree of clubbing. Her temperature was 97.4°F. The conjunctivae were injected and there was moderate exophthalmos but the eyes, ears, nose and throat were otherwise normal. The thyroid was not enlarged and there were no abnormal pulsations of the cervical vessels and no lymphadenopathy. The heart was enlarged to the left anterior axillary line with the point of maximum impulse just lateral to the mid-clavicular line but no enlargement to the right could be detected. There were no thrills or murmurs. The blood pressure was 100 systolic and 90 diastolic. The apical rate was 160 and the rhythm was regular. The lungs were negative to auscultation and percussion and the respirations were 28 per minute. The abdomen was protruberant with shifting dullness and a fluid wave present. The liver was not enlarged to palpation or percussion. There was very slight pretibial and pedal edema. The neurologic examination was negative.

The blood count was 7,430,000 erythrocytes, 24 Gm. of hemoglobin, 8,200 leukocytes with 68 per cent neutrophils and 32 per cent lymphocytes. The hematocrit was 80, the mean corpuscular volume 107 cubic micra, the mean corpuscular hemoglobin 32 micromicrograms, and the mean corpuscular hemoglobin concentration 30 per cent. The cephalin-cholesterol flocculation test was negative, as were the thymol turbidity and the serum colloidal gold. The serum protein was 6.3 Gm. per cent, the serum albumin 3.0 Gm. and the serum globulin 2.4 Gm. Blood cultures on three consecutive days were negative. The urine had a specific gravity of 1.013, and contained 600 mg. of albumin per 100 cc., with many hyaline and granular casts, numerous leukocytes and epithelial cells. The blood N.P.N. was 71.5 mg. A portable teleoroentgenogram of the chest (Fig. 1) showed the transverse cardiac diameter to measure 15.5 cm., consisting of 5 cm. to the right and 10.5 cm. to the left of the midline. The total inside transverse diameter of the chest measured 27.5 cm. The pulmonary conus was unusually prominent and the aorta had a somewhat right-sided position. There was a circumscribed mass in the right hilus area with some increased hilar markings throughout both lungs. An electrocardiogram taken shortly after admission showed right axis deviation, auricular flutter with 2:1 and 3:1 A-V block and myocardial damage. The venous pressure measured 155 mm. of water, and the circulation time from right arm to tongue was twelve seconds.

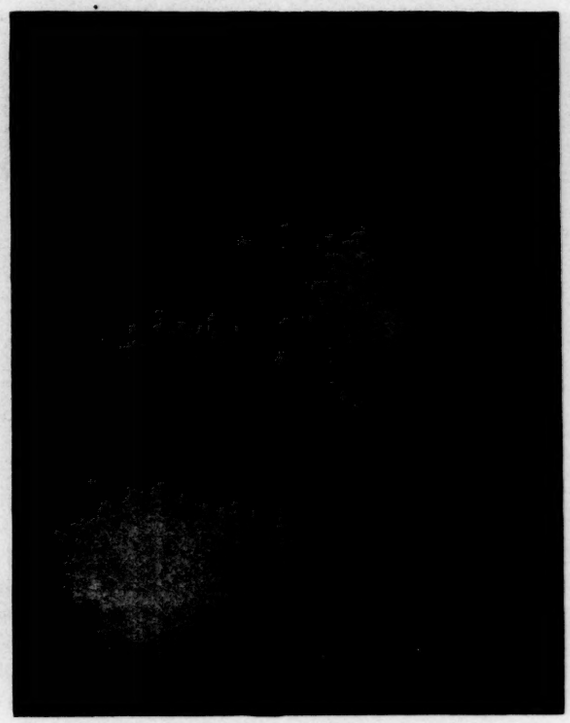

FIG. 1. Teleoroentgenogram in Case 1 showing prominent pulmonary conus, circumscribed mass in the right hilus area and the aorta in a somewhat right-sided position.

The patient received oxygen intranasally, fluids were restricted to 1000 cc. per day and she was digitalized. She was given 2 gr. of quinidine every six hours for six days beginning on the third hospital day. The patient received no other medication except analgesics and antispasmodics for menstrual cramps which lasted for two days.

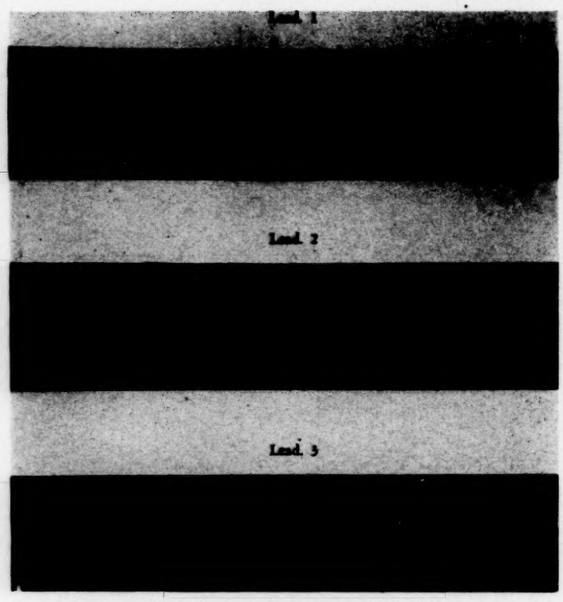

FIG. 2. Electrocardiogram in Case 1 showing right axis deviation, auricular flutter with 4:1 block.

A few hours after admission the cardiac rhythm became quite irregular and a second electrocardiogram showed auricular flutter with 2:1, 3:1 and 4:1 A-V block. On the third hospital day the apical rate had slowed to 72, and a systolic murmur and thrill were present to the left of the sternum in the third interspace. Five days after admission the electrocardiogram (Fig. 2) still showed auricular flutter but with a 4:1 A-V block. By the twelfth hospital day the patient had improved considerably and the fourth electrocardiogram showed a normal sinus cardiac rhythm with delayed A-V conduction. The following day she was feeling still better, was able to lie flat in bed, the pedal edema had entirely disappeared and the cyanosis and ascites had decreased. The cephalin flocculation was reported as 2 plus. In the evening of the thirteenth hospital day the patient suddenly became worse, gasped for breath and died within ten minutes.

The clinical diagnosis was congenital heart disease, with probable large septal defects, possible Eisenmenger complex; dilatation of right pulmonary vessels, myocardial damage, congestive heart failure, hypertrophy and dilatation, auricular flutter with 2:1, 3:1 and 4:1 block.

The body at autopsy was that of a well nourished white woman. There was a brownish induration of the lower part of the legs but no edema. The abdomen was slightly distended and there was an extreme degree of clubbing of the fingers and toes. The skin of the entire body was slightly bluish in color.

FIG. 3. Showing one large auricle in Case 1.

In the thoracic cavity the lungs were found fully expanded and there were a few pleural adhesions on the right side but no increase in the amount of pleural fluid. The cardiac area was slightly rounded and increased in transverse diameter. The pericardial sac was smooth and glistening and the pericardial fluid was normal in color and amount. The heart together with the thoracic aorta weighed 650 Gm. The pulmonary artery originated in the usual anterior position but was markedly widened in such a manner as to produce a large conus. The aorta, which was smaller than normal, originated just posterior and to the right of the pulmonary artery, extended upward in the usual manner to form a normal arch and descending thoracic aorta. At the mid-portion of the arch of the aorta a direct connection between the aorta and the distended main portion of the pulmonary artery was found, evidently a ductus arteriosus patent to a diameter of 1 cm.

The auricular portion of the heart (Fig. 3) consisted of one large chamber approximately

equal in size to two normal auricles, and divided into right and left sides by only a very thin strand of muscle tissue. The inferior and superior venae cavae entered the right side of the auricle in the usual manner, and the pulmonary veins entered the left side in approximately normal positions. Through a normal tricuspid valve the right portion of the auricle communicated with a greatly enlarged and hypertrophied right ventricle. From the latter chamber a normal pulmonary valve opened into a greatly enlarged pulmonary artery. The dilated pulmonary artery bifurcated into a right and left branch and the left branch was of unusual diameter and thickness. The right pulmonary branch was enlarged just distal to its origin and measured 4½ cm. in diameter as it entered the lung. The vessel was quite thickened, filled with recent hemorrhagic material and was lined by a laminated, dried, yellow clot in the manner of a true aneurysm. This aneurysmal dilatation extended well into the root of the right lung and downward into the lower lobe for a distance of 8 cm. before reverting to a normal caliber. The left portion of the auricle opened into a very small and almost rudimentary left ventricle through a mitral valve situated directly above and slightly posterior to the tricuspid valve. The left ventricle gave rise to the aorta through an aortic valve which was anatomically intact but rather small.

In the lungs there were areas characteristic of chronic passive congestion. The liver was 3 cm. below the right coastal margin, and the cut surface of the liver showed a moderate degree of congestion. The mesenteric vessels were engorged and both the serosal and mucosal surfaces of the small intestine were mottled and hemorrhagic. The kidneys and spleen were congested but otherwise normal.

The diagnosis was cor triloculare biventriculare with rudimentary left ventricle, hypertrophied right ventricle, widely patent ductus arteriosus, dilatation of the pulmonary artery, aneurysm of the right pulmonary artery and hypoplasia of the aortic valve and the aorta.

Case II. Baby girl L. was delivered by low forceps under cyclopropane anesthesia after a normal period of gestation. The mother had one other child who was normal. The baby's respirations started spontaneously after birth but it was cyanotic, and this persisted in spite of oxygen inhalations. Examination at that time failed to reveal any murmurs. The cyanosis was most

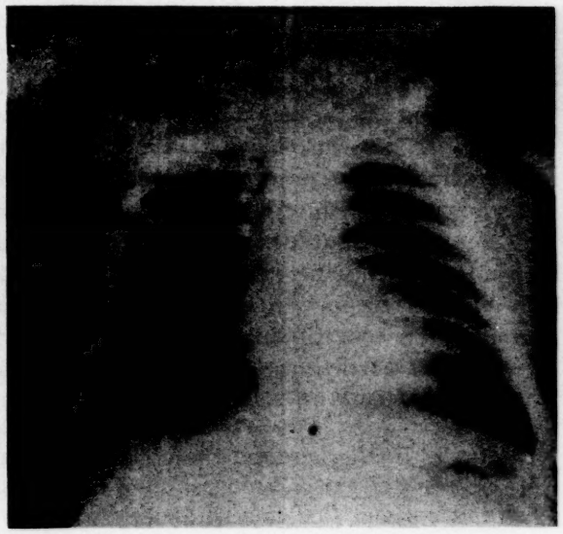

Fig. 4. Teleorentgenogram in Case II.

pronounced when the baby cried or exercised. She ate fairly well, respirations were regular and the temperature remained normal. The heart rate was usually around 170 per minute. The electrocardiogram showed sinus tachycardia and right axis deviation. The teleoroentgenogram (Fig. 4) of the chest revealed the heart to be slightly enlarged to the left and the cardiac shadow was definitely not the normal infant contour. Other laboratory studies were not remarkable. The baby was treated with digitalis and oxygen but showed no improvement. On the sixth hospital day the liver was 3 cm. below the right costal margin. Eight days after delivery a faint systolic murmur was heard over the lower part of the sternum, and on the tenth day this murmur was louder and a thrill was palpable over this area. On the fifteenth day of life the respirations became labored, the cyanosis deepened and the temperature started to rise. The child remained in very poor condition until its death on the twentieth hospital day. Clinical diagnosis was congenital heart disease, type not definitely determined but possibly a two- or three-chambered heart, myocardial damage, hypertrophy, dilatation and congestive failure.

Autopsy findings revealed generalized moderate cyanosis of the skin. The lungs were partly obscured by a markedly enlarged cardiac mass which measured 8 cm. at the widest diameter. The great vessels were found to originate from the heart in the usual manner, except that the enlargement of the heart had caused the organ to be situated in a somewhat transverse position forcing the vessels to extend vertically in the

midline. The heart had a single auricle which was rather small in relation to the large size of the ventricles. This auricle had two laterally placed auricular appendages but there was no division between them, the interauricular septal defect being practically complete. Four pulmonary veins came directly from the lungs and entered this auricle, two on the right and two on the left side. Both ventricular walls showed hypertrophy but all four valves were normal. A patent ductus arteriosus extended between the aorta and the pulmonary artery which were normal in course and distribution.

The remainder of the body revealed no further abnormality and the microscopic sections were negative except for congestion of the lungs, liver and spleen. The final diagnosis was congenital heart disease consisting of cor triloculare biventriculare with patent ductus arteriosus, hypertrophy of both ventricles, rotation of the great vessels and the presence of four pulmonary veins opening into the common auricle.

Case III. Male baby D. was born after a ten month but otherwise normal period of gestation. The delivery was spontaneous and normal in every respect. Examination just after birth revealed a harsh precordial murmur and aside from a small left hydrocele there were no other positive findings. The infant took nourishment well, gained weight and had no apparent difficulty until the eighth hospital day when he became lethargic, cyanotic and the respiratory rate increased to 50 per minute. At this time the temperature was 95.6°F. and the heart rate was 130 per minute. The precordial systolic murmur previously noted had not changed. The right lung was clear but the left was dull to percussion and moist inspiratory rales were heard over the left base posteriorly. The liver was not enlarged and there was no dependent edema. It was thought that the baby had lobar pneumonia and some type of congenital heart disease. A teleoroentgenogram of the chest taken later the same day showed most of the thoracic cage to be occupied by the heart which was enlarged both to right and left. The blood count was 4,090,000 erythrocytes, 14 Gm. of hemoglobin, 18,400 leukocytes with 62 per cent neutrophils, 37 per cent lymphocytes and 1 per cent monocytes.

The following day the cyanosis was less intense but the moist rales were still present in the left base, and a diastolic component to the murmur was now heard over the precordium. The baby expired on the ninth day after birth. The clinical diagnosis was left lower lobar pneumonia and congenital heart disease, type undetermined.

At autopsy the body was extremely cyanotic but the skin was otherwise normal except for a hemangioma between the eyes and extending over the right eyelid. The brain was somewhat edematous. The cardiac area was considerably enlarged, measuring 9½ cm. in the widest diameter and the pericardium was smooth, glistening and contained the normal amount of fluid. On the epicardial surface of the heart there were several petechiae, the largest measuring 2 mm. in diameter. The heart measured 8½ cm. in widest transverse diameter and weighed 90 Gm. It consisted of three chambers: a large common auricle in the position usually occupied by the right auricle, a very large right ventricle and an extremely small left ventricle. In the single auricle were located the openings of the pulmonary veins and the venae cavae. What appeared to be the tricuspid valve was situated between the right ventricle and the auricle but no structure corresponding to the mitral valve could be identified. The pulmonary valve and the pulmonary artery were normal in position and form, as were the aortic valve and the aorta. The coronary orifices were identified within the sinus of the aortic valve. There was also a large interventricular septal defect just below the pulmonary and aortic valves. An examination of the remainder of the body revealed bilateral congestion of the lungs and three small intussusceptions of the jejunum.

The final cardiac diagnosis was congenital heart disease consisting of a common auricle, a large right ventricle, a small left ventricle with an interventricular septal defect and absence of the mitral valve.

Case IV. Male baby W. was born to a seventeen year old primipara after a normal gestational period. The delivery was a frank breech extraction under cyclopropane-oxygen anesthesia. An examination shortly after delivery failed to show any abnormalities. The baby's progress for the first few days after birth was only fair since he never took over one-half ounce of formula at a time. He had a subnormal body temperature even though he was placed in an incubator. There were, however, no significant findings on repeated examinations during this period. Six days after birth the baby suddenly became cyanotic over the entire body and he

began to have respiratory difficulty. At that time the cardiac rate was rapid, the tones were somewhat faint but no murmurs were heard and no thrills palpated. The liver was three fingers below the right costal margin and one finger below the left costal margin. The abdomen felt doughy and was slightly distended but no masses or organs except the liver were palpable. The lung findings were normal except for rapid and shallow respirations. There was very slight dependent edema.

The infant was treated with oxygen inhalations and external heat; however, the baby died early in the morning of the seventh hospital day. The cyanosis increased considerably during the few hours prior to death. The clinical diagnosis was congenital heart disease with a probable septal defect so large that it produced no murmurs.

There was very deep lividity and cyanosis of the skin of the entire body at autopsy examination. The heart was greatly enlarged in the transverse diameter and the aorta and pulmonary arteries were normal except for rotation posteriorly and to the right due to enlargement of the heart. The atrial portion of the heart consisted of a single chamber in which a median bar of tissue represented the only demarcation between right and left auricles. The left ventricle was enlarged but the mitral, aortic, tricuspid and pulmonary valves were normal. Directly beneath the aortic valve was a defect in the interventricular septum which measured 8 mm. in diameter. The right ventricle was increased in size and its musculature was thicker than normal. The remainder of the body was normal.

The anatomic diagnosis was cor triloculare biventriculare with a defect of the interventricular septum.

COMMENT

Including these four cases a total of seventy-seven cases of cor triloculare have been reported in the literature to date, of which twenty-two were biventricular and fifty-five biatrial. The four cases reported here were all biventricular. Although Taussig[28] has stated that the occurrence of two or more malformations in one heart is rare, this series is in accord with our experience that congenital cardiac anomalies are usually multiple rather than single. In this series there were thirteen instances of patent ductus arteriosus, fourteen defects of the pulmonary artery, thirteen defects of the aorta, four dextropositions of the aorta, fourteen valvular defects, three coarctations of the aorta, five cases of transposition of the great vessels, one persistent truncus arteriosus and one aneurysm of the pulmonary artery. A large proportion of these cases had defects of the portion of the cardiac septum which was present and actually functioned as bilocular hearts.

Complete information was available in thirty-eight cases and of these, murmurs were present in nineteen and cyanosis in thirty-four. All of the four cases reported here were cyanotic and in three there was a systolic murmur. As in cor biloculare, electrocardiographic and roentgenologic studies are of little assistance and the presence of other cardiac defects renders the clinical diagnosis of the lesion extremely difficult. However, if the injection of radiopaque substance and circulation time reveals the presence of a septal defect with no thrill felt or murmur heard, the probability of cor biloculare or triloculare should be considered. A systolic murmur heard at all areas without the presence of a thrill has about the same probability, whereas cyanosis is of no help in making the diagnosis. Catherization of the heart, however, should be a great aid in the identification of this congenital lesion.

The first case reported here is of particular interest because it was complicated by an aneurysm of the pulmonary artery which is rather rare. Deterling and Clagett[27] reviewed the literature and found only eight cases in a series of 109,571 autopsies. They listed as one of the causes of the anomaly, pulmonary hypertension as the result of certain types of congenital hearts. Cor triloculare was present in this case together with a very large patent ductus arteriosus which made it possible for the patient to lead a fairly active life until thirty-five years of age.

Cases I and III were similar in that they both had a common auricle, large right ventricle, small left ventricle and patent ductus arteriosus; and dissimilar in that

Case III had a ventricular septum defect. Both showed cyanosis and dilatation of the superior vena cava as a result of the common auricles; and while the ductus arteriosus was patent in both, Case I had no murmur or thrill (probably due to the great size of the ductus arteriosus), while in Case III the systolic and diastolic murmurs were probably due to the smaller size of the ductus arteriosus and the ventricular septum defect. Case I lived thirty-five years and Case III only nine days probably because while both practically functioned as biloculare hearts, the small left ventricles contributed somewhat to the circulation, the former in a normal manner from the common auricle and in the latter by blood received from the ventricular septum defect since the mitral valve was absent. The difference in life span appeared to be because in the infant the ductus ateriosus did not dilate rapidly enough to maintain an adequate systemic circulation, whereas in the thirty-five year old woman it did. This was shown on the roentgenograms by the absence in one and the prominence in the other of a pulmonary conus, but at that time the significance was not realized.

Further comparison revealed that dilatation of the superior vena cava is not a constant finding of a large auricular septum defect or single auricle because it was present in only two of the four cases. It was present in Case I probably because of the greatly increased pressure in the right heart that resulted from maintaining both the greater and lesser circulations, and in Case III it may have been due to the absence of a mitral valve. It is noteworthy that none of the patients had pulsation of the liver. All had cyanosis as the result of a common auricle regardless of other lesions.

Cases II and IV were similar in that they both had a common auricle and two large ventricles, and dissimilar in that Case II had a patent ductus arteriosus and Case IV had a ventricular septum defect. In the former the systolic murmur and thrill was probably due to the patent ductus arteriosus, which was closed in Case IV. This latter case had no murmurs or thrills but had a ventricular septum defect. Both of these hearts functioned as three-chambered organs. Everything else being equal there appears to be no advantage in cor triloculare biventriculare, of a functional three-over two-chambered organ, except that a large patent ductus arteriosus is not necessary to maintain both circulations. This suggests the possibility of surgical benefit by anastomosis of the pulmonary artery and the aorta.

SUMMARY

Four cases of cor triloculare biventriculare are reported with a discussion of the signs, symptoms and possible methods of diagnosis antemortem.

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Observations on Small Intestinal Hypomotility and States of Hypertonicity Arising from Functional Bases*

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THE causes for delay in the emptying of the small bowel are only partially understood. In 1938 Wright and I[1] described a group of patients in whom barium sulfate was present in the ileum fourteen hours after its oral administration.

TABLE I
INDICATING RELATION OF SYMPTOMS OSTENSIBLY OF GASTROINTESTINAL ORIGIN TO SMALL INTESTINAL HYPOMOTILITY

Symptoms	No. of Patients with X-ray Evidence of Small Intestinal Hypomotility		No. of Patients without X-ray Evidence of Small Intestinal Hypomotility
	After a 14-hour Fast	After a 14-hour Fast Plus a Two-hour Post-prandial Period	
Not suggesting intestinal origin.....	0	3	47
Suggesting intestinal origin			
(a) Lower right quadrant abnormality.....	6	48	38
(b) Functional basis.....	15	23	67

Most of the patients looked well. Many complained vaguely of abdominal distress although their symptoms and signs did not form a distinctive pattern. The patients were fed an average breakfast fourteen hours after the barium meal. In most of the patients the barium was expelled from the ileum one or two hours after this second meal. In some, however, the barium remained in the ileum and we believed that this was indicative of the presence of partial organic obstruction of the small intestine. This view was confirmed at operation in ten of twelve patients.

Since this first report roentgenologic examinations of the small intestine have been made in 247 patients. (Table I.) In 152 of these patients the small intestine was free of barium fourteen hours after a barium meal; some of this group had symptoms suggestive of partial intestinal occlusion but this was not subsequently confirmed. In twenty-one patients barium was retained in the small intestine fourteen hours after it was swallowed but was expelled one or two hours after breakfast. One of this group is included among the patients discussed later, but at a group these patients were without significant symptoms. Finally, there were seventy-four patients in whom barium remained in the ileum fourteen hours after its oral administration and was not then expelled by eating the test meal. On clinical grounds forty-eight of these patients were thought to have organic disease of the small intestine. In the remaining twenty-six patients, however, no evidence of organic disease of the small intestine was detected. In sixteen of these twenty-six patients the roentgenologic studies were repeated a second time, and in each instance the diagnosis of intestinal

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hypomotility was confirmed. The clinical features of these twenty-seven patients have been reviewed in an attempt to evaluate the significance of this hypomotility.

METHOD

Various parts of the small intestine give x-ray patterns with differing characteristics. That of the jejunum is characterized by a herring-bone effect that is representative of this part of the bowel.

As barium courses through the lower reaches of the small intestine, it becomes more concentrated due to water absorption. Since the rate of peristalsis decreases progressively below the pylorus, the passage of the barium slows and this substance tends to collect within a diminishing length of the intestine. As a result, radio-opaque material accumulates in the lower ileum, often as a non-descript mass which is difficult to interpret.

In order to study the lower loops of the small intestine recourse may be made to several methods of investigation. Serial examinations may be made during the day in which barium is administered by mouth. When films are made at frequent intervals, a fairly complete representation of activity is presented and various stages of contraction and relaxation are noted. During the study it is generally possible to delineate the last few feet of the small bowel. Beneath the fluoroscope active peristalsis may at times be seen; contraction of the bowel can be noted in some areas, relaxation in others. The entrance of the ileum directly into the cecum is frequently seen as barium passes through the terminal inches.

A good view of the lower loops of the ileum may often be obtained following the instillation of barium by enema. In the majority of instances the ileocecal valve will relax to permit the entrance of varying quantities of barium into the small bowel. The pattern obtained by this method is strikingly different from that obtained when the opaque substance is given by oral administration. The barium which reaches the ileum by enema is in a more fluid state.

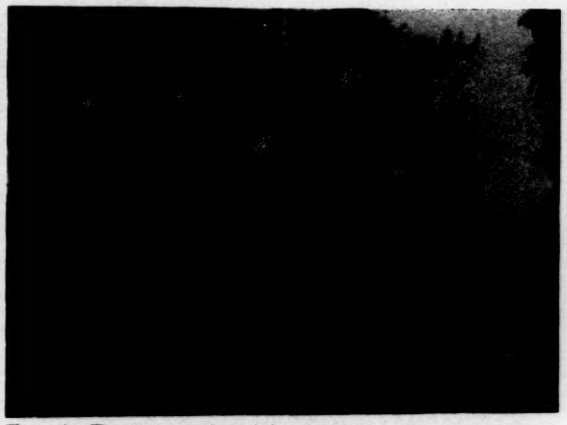


FIG. 1. Demonstrating jejunum pattern; the gastroenterostomy opening is seen at upper right.

As a result the mucosal pattern is often well depicted and generally the loops appear larger, probably because they are relaxed under the pressure of fluid entering them in a retrograde manner.

There is a third method of study which was mentioned above and which we have found very helpful. It may be utilized only on patients whose stomachs empty in less than five hours. Barium sulfate is given to the patient about three hours after a light supper. Following this he fasts and presents himself for examination the next morning, approximately fourteen hours after the ingestion of barium. The unobstructed small intestine will have emptied itself by then in the majority of individuals. If barium is seen in the terminal ileum, the patient may be given breakfast, following which his lower bowel is again studied. If it still contains barium, one may regard the retention as significant. In fact, one may regard the presence of barium within the fasting terminal loops with suspicion, but for the sake of security this study, with one exception, includes cases only in which there is retention following breakfast.

To acquaint the readers with the visual aspects of some of the conditions that have been of interest, a few illustrations are presented.

Figure 1 is an example of the pattern of a normal upper jejunum showing the herring-bone pattern. This patient had had a partial gastric resection for a duodenal

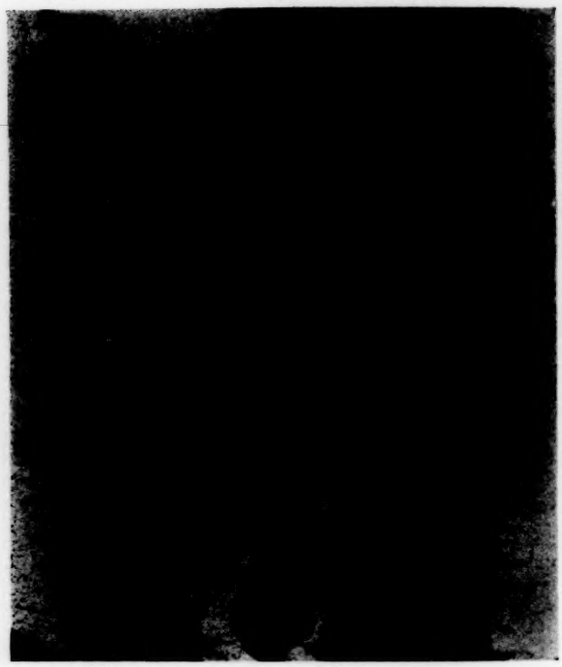


FIG. 2. Film made one hour after ingestion of barium; the small bowel is outlined throughout its length, and the cecum is partially filled (film was reversed when printed; hence what now appears as the right side is really the left side).

ulcer about eighteen months previously, and the unimpeded entrance of barium into the jejunum gives an excellent example of its markings.

Figure 2 shows the loops of almost the entire small intestine; and although only an hour has elapsed since the ingestion of barium, considerable dehydration has occurred in the lower ileum. In this presumably normal individual barium is seen entering the cecum at this time. Study of the figure reveals illustrations of varying stages of concentration of the barium and various phases of peristalsis with excellent delineation of the mucosal pattern at various levels of the small bowel.

In Figure 3 much of the barium lies within the cecum five hours after ingestion. This is a common occurrence in the normal individual. However, there are numerous instances in which a relatively large amount of barium at this time lies within the loops of the small intestines that occupy the pelvis.

It has generally been believed that two to three hours is the time elapsed in the

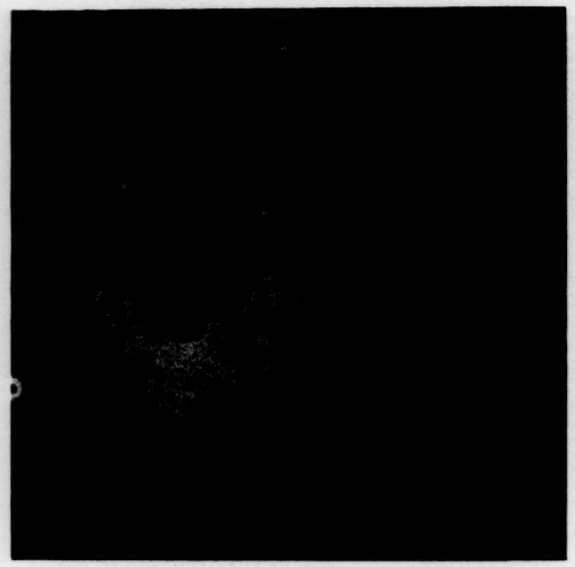
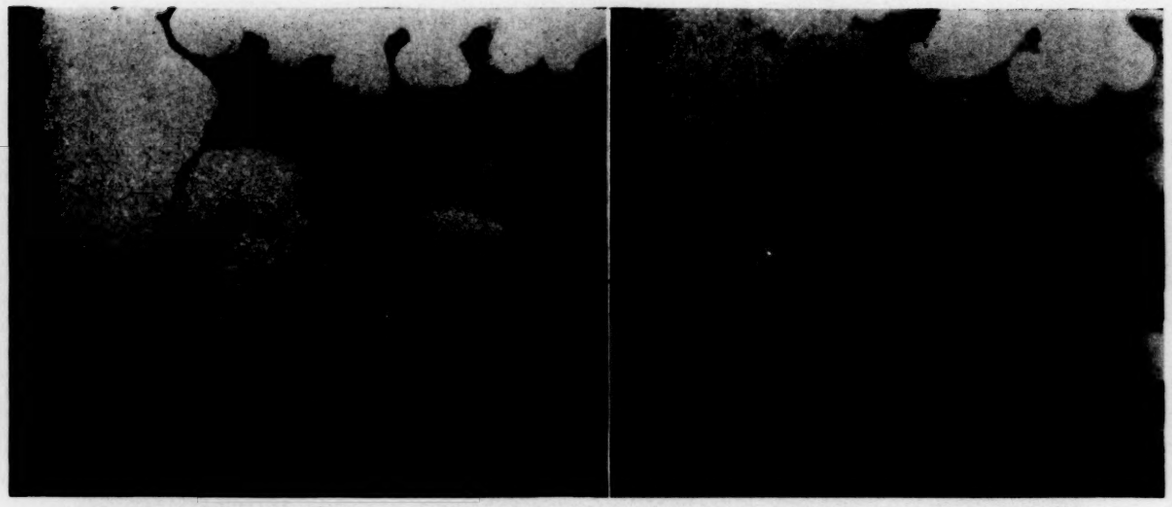


FIG. 3. Film made five hours after the ingestion of barium which is mostly collected in the loops of the terminal ileum and the proximal portion of the large bowel; the ileocecal area is well defined.

passage of the head of the column of barium from the stomach to the ileocecal valve. We have found a number in which no more than an hour was needed to effect entrance to the cecum. It would seem quite likely that an irritable tract would increase the speed. This we have also found to be true. Many investigators state, and the idea is generally accepted, that the gastrointestinal tract of a healthy individual will clear its small bowel of barium in eight to nine hours. The writer has no observation that would suggest otherwise.

PRESENTATION OF DATA

The physical examination of the patients revealed no evidence that any of them was suffering from an acute or chronic disease that might influence motility or tone. They were not emaciated nor were they obese. The majority of them conveyed to the examiner the appearance of physical well being. Their laboratory studies were not indicative of important abnormalities. In none was the abdominal examination suggestive of intraperitoneal disease or partial obstruction to intestinal motility. There were eleven women and sixteen men whose studies are included in this group and their



4 5

FIG. 4. Barium remaining in the loops of terminal ileum fourteen hours after the ingestion of barium.
FIG. 5. Follow-up of Figure 4 two hours after breakfast; most of the barium has entered the cecum but a small amount remains in the terminal ileum.

ages varied from twenty-six to sixty-one. They were all patients from a private practice and of the white race. Barium left their stomachs in less than five hours.

As it is not feasible to present in detail the studies on the twenty-seven patients, the histories and x-ray studies of seven patients who are representative of certain types of conditions will be presented.

The first patient to be presented was one of the earlier cases studied. His findings indicated the need for more careful consideration of a functional basis for ileostasis. He was a healthy looking man aged forty-one years who claimed great discomfort in his lower right quadrant. His history and behavior pattern gave every indication that he was emotionally unstable. His physical examination was negative, except for tenderness on palpation at the ileocecal area. His x-ray films made fourteen hours after the ingestion of barium showed an important retention of barium in the ileum. (Fig. 4.) Figure 5 shows that most of the barium was passed into the cecum following a meal, showing the stimulating effect of food upon peristalsis. We did not believe that there was clinical evidence of organic disease, but were not certain enough to assure the patient he did not need an operation. The studies up to that time, which had been made on several patients with similar clinical findings, had indicated their symptoms were caused by diseased appendixes or local intestinal adhesions or both. At operation and biopsy the appendix was found to be normal and the ileum was free of adhesions.

The next patient is representative of a group of eight whose symptoms were not necessarily those of gastrointestinal origin. They were overworked and tired; their fatigue was the result of consistant application to a type of work that demanded too much of them. Five of these patients complained of indigestion which was characterized by postprandial fullness, heaviness, gas and abdominal distention; eructation was common. A fourteen-hour ileostasis was found in each of them. The propulsive effect of food did not clear the bowel of barium.

The man, selected as a typical example, was fifty years of age, a salesman who traveled from town to town by automobile. His ambition was to sell more window shades than any of his competitors. He may have been succeeding but, as he admitted, the effort was fast exhausting him. He suffered from indigestion, gas and abdominal distention. His lower abdomen was uncomfortable. His x-ray findings are illustrated in Figures 6 and 7. A second study revealed similar findings.

This patient was given the treatment which his complaint and physical findings so urgently indicated, namely, rest. After a period of three weeks he returned to work refreshed, free of symptoms and with small intestines that emptied within the accepted normal period of hours.

We have seen the same type of delay in four patients with low basal metabolic rates and with cholesterol serum blood levels above 250

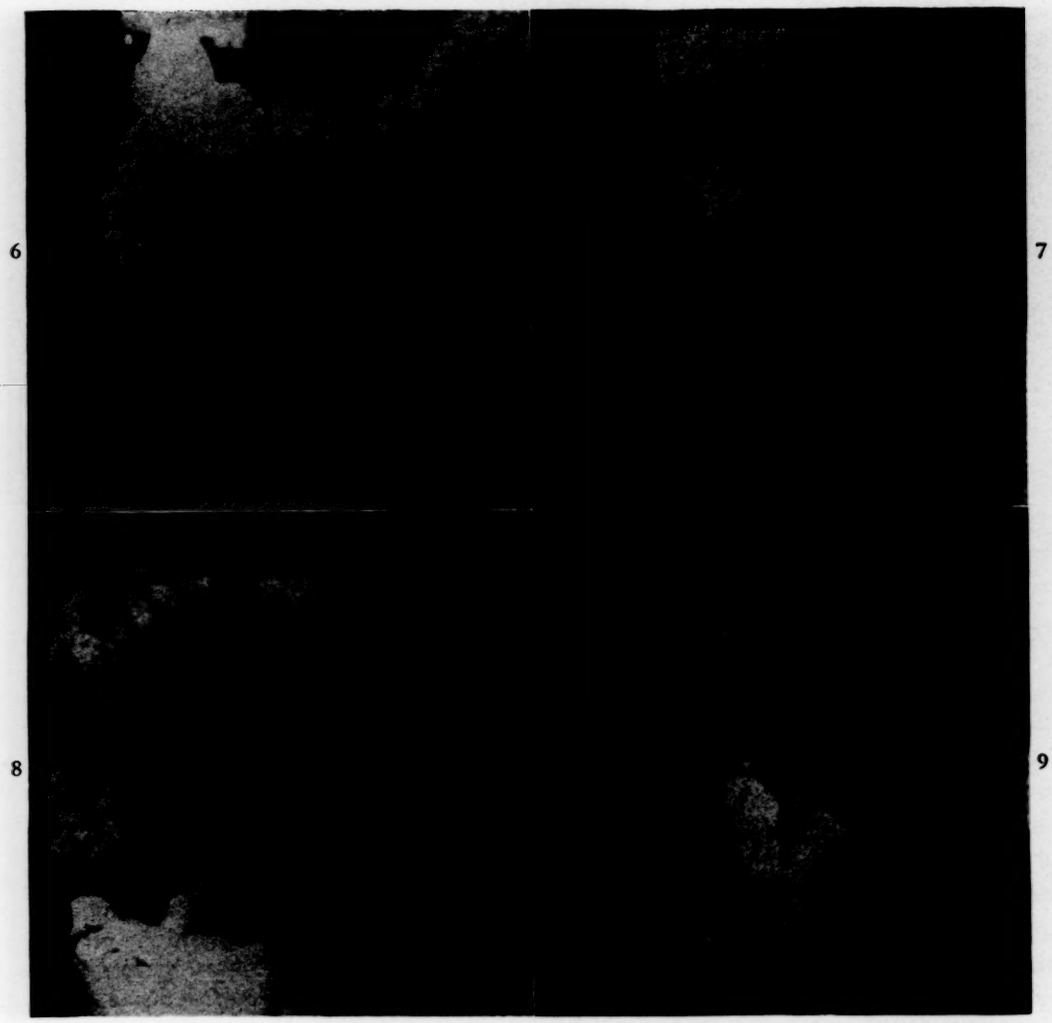


FIG. 6. Fasting film made fourteen hours after ingestion of barium; the loops connected with the cecum and lying to the left of the midline are the ileum; fatigue state.
FIG. 7. Continuation of Figure 6; film made two hours after breakfast showing important residue in terminal ileum and evidence of recently passed peristaltic wave at the ileocecal junction.
FIG. 8. Film made fourteen hours after ingestion of barium; by fluoroscope it was determined that the barium in the lower left quadrant was in the small bowel; basal metabolic rate was −30 per cent.
FIG. 9. Continuation of Figure 8; film made two hours after breakfast showing large barium residue in small bowel.

mg. per cent. The ages were between thirty-two and fifty-one years. Two of these patients were women. The pertinent x-ray studies of one patient are shown in Figures 8 and 9. This patient, whose age was fifty-one years, was a member of Congress. He was accustomed to the wear and tear of such a life, but for several months he found that he tired easily, that it was increasingly difficult to drive himself to work and that his abdomen did not feel normal. His general physical examination was not remarkable. His basal metabolic rate was repeatedly—25 per cent or below and his serum cholesterol was 400 mg. per cent. X-ray studies revealed a large amount of barium in the ileum at the end of fourteen hours. The stimulus of food gave little if any propulsive effect. After thyroid medication his basal metabolic rate approximated the normal and it was impossible to find x-ray evidence of ileostasis. Only three of this group were studied by x-rays following thyroid medication. The motility of their small intestines returned to normal.

The next two patients to be presented were both emotionally unstable; they are representative of fifteen other patients with positive x-ray

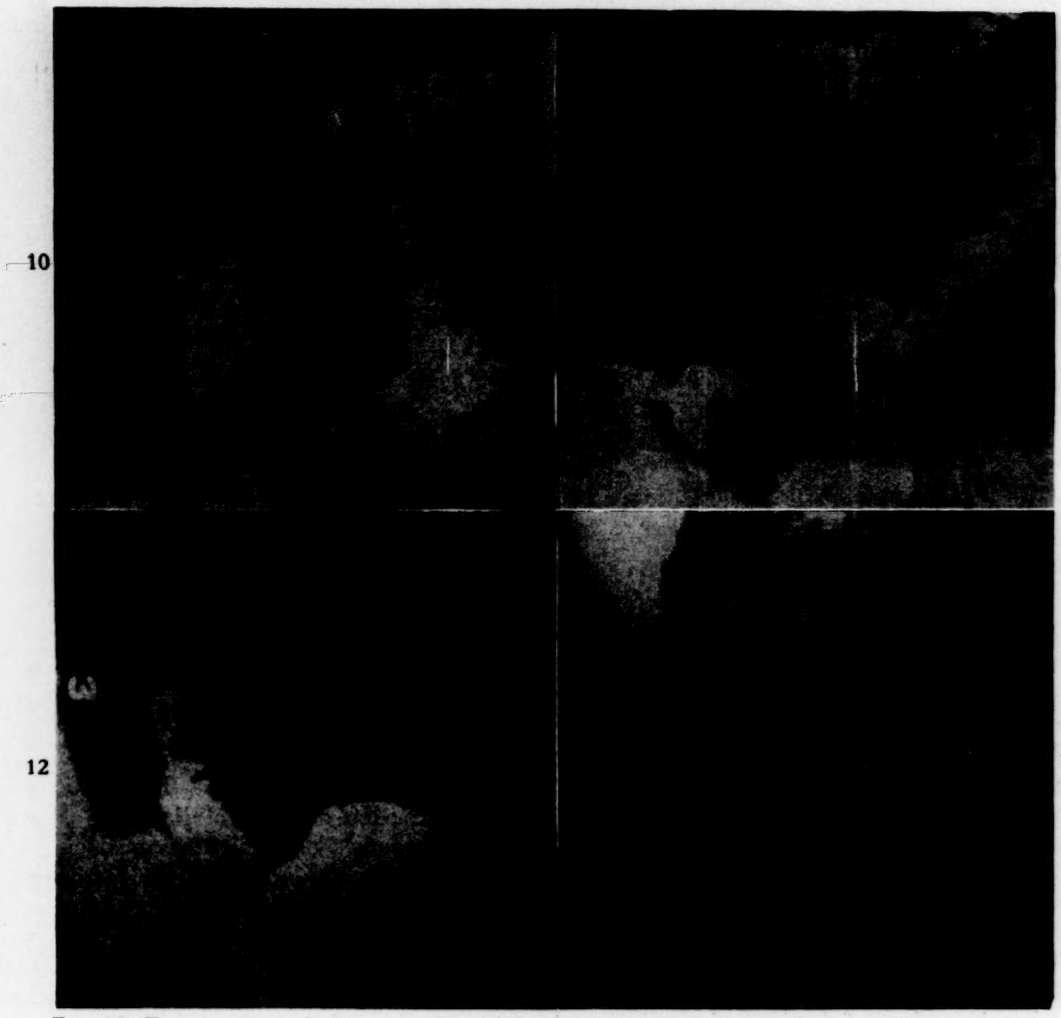


FIG. 10. Fourteen-hour fasting retention of barium in terminal ileum; the patient was a greatly agitated woman, age twenty-nine years.
FIG. 11. Continuation of Figure 10 showing barium remaining in terminal ileum two hours after breakfast.
FIG. 12. Film made three hours after ingestion of barium showing spastic terminal ileum with cecum beginning to fill; patient was a depressed, agitated male teacher.
FIG. 13. Same patient as in Figure 12; the film was made sixteen hours after ingestion of barium and two hours after his fast had been terminated by the eating of breakfast. The same type of spasticity noted in the previous film is also demonstrated here.

findings. The patients in this group all complained of symptoms that seemed to arise from their gastrointestinal systems. The woman, whose age was twenty-nine years, was in the midst of an agitated state. She complained of frequent, small, firm, daily bowel movements and of intestinal cramps. The man had been through a long period of depression in which symptoms of indigestion had played a prominent part. His health had returned to a point at which he was just beginning to adjust himself to the thought of work. Both were teachers.

A fourteen-hour x-ray film which shows ileostasis in the woman is shown in Figure 10. It gives a good view of relaxation of part of the terminal ileum after what may have been a propulsive movement. The next film (Fig. 11) was made two hours after eating. Following food stimulus the proximal terminal ileum entered into spasm and little or none of the barium had entered the cecum. Within a period of two years three similar x-ray studies were made on this woman; they all showed small intestinal hypomotility and hypertonicity. The pains experienced by this patient were so strong that it was only with great difficulty that she was kept

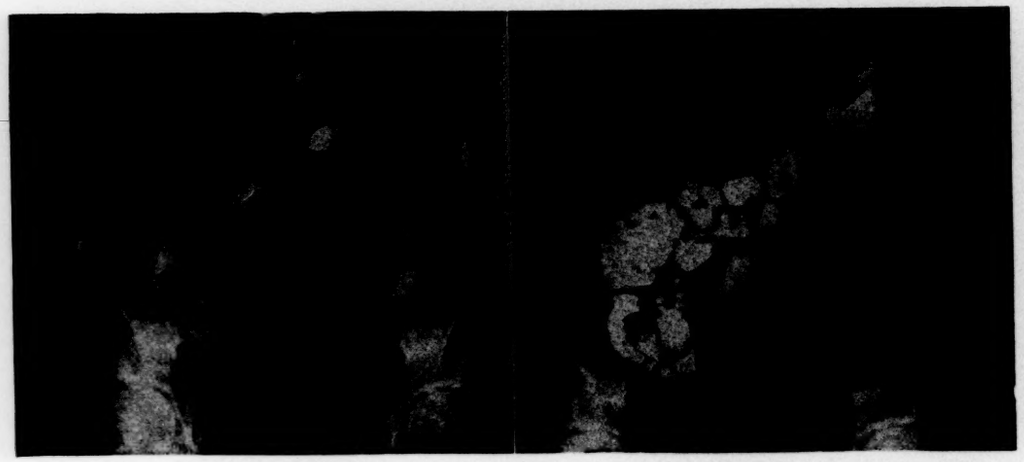


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FIG. 14. Film made five hours after the ingestion of barium. The stomach had emptied itself and all the barium ingested is seen in this film. It was believed the patient had an organic partial small bowel occlusion.

FIG. 15. A second study made on patient in Figure 14; the film was made five hours after the ingestion of barium and again it was considered that the patient had an organic partial occlusion. At operation no lesion was found.

out of the hands of surgeons. Psychotherapeutic treatment finally gave her the power to gain some measure of control over her emotional instability, and the x-ray films of her intestines made after a long period of psychotherapeusis revealed no ileostasis.

Figures 12 and 13 made of the male teacher, whose age was 41 years, are representative of those made on four patients. In the three-hour film one sees the effect of spasm extended over 12 or more inches of the terminal ileum. On another occasion x-ray films made fourteen hours after ingestion of barium showed ileostasis and the same extent of spasm. This ileostasis remained two hours after eating. The films gave good evidence of no loss of contractibility, so it would seem reasonable to believe that the propulsive action of the stimulus of food was not strong enough to force the contents of the bowel through the spastic area within the period of time of the investigation.

This patient was operated upon as his symptoms and signs suggested some inflammatory reaction about the appendix or the presence of adhesions involving the terminal ileum. At biopsy the condition of the intestinal viscera was considered normal. For some months after the operation he remained in an agitated state of mind; this is another demonstration of the importance of not operating on an emotionally unstable patient unless he is faced with an emergency.

The history and studies of two other individuals are presented in some detail as they further illustrate the degree to which spasm of the small bowel can attain.

A man of sixty-one years of age gave as his complaint abdominal pain. He indicated the area to the left of the umbilicus as its locus. It usually occurred an hour after meals and it was frequently quieted by eating. Through the years he had seen a large number of doctors and he had received a number of diagnoses, among which the most common was neurosis. Others concerned some malfunction of the stomach. Conversation with the patient left no doubt as to his emotional instability and introspective proclivities. Physical examination revealed no striking abnormality. He was slender but not malnourished. His loquaciousness made uninterrupted examination difficult, but he always indicated an area above and to the left of the umbilicus as the locus of his pain. Several studies were made of his gastrointestinal tract on films exposed to x-rays. Nothing abnormal was noted in the stomach. There was an area in the small intestine which delayed the passage of barium. Proximal to this area (Fig. 14) was a dilated loop. The reading of the films follows:

"There is no evidence of a lesion within the upper portion of the small intestine. However, as barium passed through the ileum, at a time approximately five hours after ingestion, it entered into a dilated loop of small bowel which contained some gas. The intestine in this region was approximately twice the diameter of the

16 17

FIGS. 16 and 17. Films made two and five hours after the ingestion of barium. The patient, age forty-one, suffered from a well defined Parkinson's syndrome. The hypertonicity of the small bowel is evident. At the end of fourteen hours a small amount of barium remained in the terminal ileum. Figure 17 shows the small intestine five hours after ingestion of barium; continuation of spasticity shown in Figure 16.

normal portion; the lower border which appeared to be the outlet of this loop was irregular and seemed to be the sight of a lesion which is partially obstructing the flow of barium. In the twenty-four hour film the small intestine is empty." The same findings were noted when the studies were repeated. (Fig. 15.)

Although the neurasthenic tendency of the patient was well recognized, the patient was operated upon with the expectation of finding peri-intestinal adhesions or an intramural tumor. The operator found no organic involvement of the gastrointestinal tract and referred to the situation as follows: "The entire small bowel was examined. No organic lesion was found in the walls nor were adhesions seen. The only abnormality noted was the presence of pronounced spasms in some sections of the ileum. The circumference of the bowel in these areas was markedly reduced."

Following operation the patient did well. One day he received an intramuscular injection of prostigmine and straightway redeveloped his previous pain; it persisted for several hours. A few days later the same drug was administered with similar results. An intramuscular injection of 10 mg. of dibutalin gave him prompt relief. Since that time the patient has received extensive directive psychotherapy and has been enabled to understand how the intestinal spasm has been the result of his emotional state. This insight has enabled him to adjust himself better; as a consequence, his pain occurs with comparative infrequency. X-ray films made subsequently have not revealed small bowel obstruction or evidence of delayed emptying.

In the beginning of the paper reference was made to rapid passage of barium through the small intestine. Serial x-ray films were made of the small bowel of a male patient who for some years had suffered from Parkinson's disease, presumably postencephalitic. The patient was forty-two years of age and he presented himself for study because of recurrent episodes of discomfort, at times approximating pain, in the lower right quadrant. Physical examination of the abdomen revealed nothing noteworthy. There was bilateral tremor of the arms, unilateral tremor of the legs and also moderate rigidity of the muscles. Examination of the films of the small bowel revealed barium in the cecum one hour after ingestion, and at this time the stomach contained only a trace of barium. It also revealed pronounced contractions of extensive areas of the ileum. (Figs. 16 and 17.) At a later date an x-ray examination revealed that a small amount of barium remained in the terminal ileum at fourteen hours; following the propulsive stimulus of food it disappeared. It would appear that the excessively spastic state of the small bowel may have been the cause of this retention.

COMMENT

In recent years emphasis has been attached to the influence of emotional states on the stomach, pylorus and colon. How-

ever, little or no attention has been paid to the effect of the psyche on small intestinal function. Evidence has been presented above that hypomotility of the small intestine may be related to emotional factors. Twenty-seven patients have been described in whom ileostasis was detected roentgenologically in the absence of organic disease. Some of the patients were chronically fatigued, both physically and mentally; intestinal motility returned to normal after a period of rest. In others hypomotility of the small intestine was associated with an abnormally low basal metabolic rate and abnormally high concentration of serum cholesterol. Hypomotility of the ileum disappeared when these patients were treated with thyroid extract. However, the effect of thyroid extract was not tested in those patients with ileostasis whose metabolic rates were normal. Other patients had anxiety or tension states. In these patients hypertonicity of the small intestine and spasm of the ileocecal junction may have been present. Golden[2] described small intestinal hypomotility in patients with vitamin deficiency states. In none of the patients in the present study was there evidence of vitamin deficiency.

The cases which have been described illustrate the importance of the differentiation of organic and functional causes for ileostasis. Recognition of the functional nature of many cases of ileostasis may spare patients needless surgery. In these patients psychotherapy directed against the problems responsible for their tension state may be followed by satisfactory improvement in the motility of the small intestine.

SUMMARY

Data are presented on x-ray evidence of small intestinal hypomotility noted in twenty-seven patients. The delay was not considered to be the result of organic intestinal or peri-intestinal disease. Evidence is presented to indicate that the delay was the result of functional states, which reduced small intestinal motility or altered small intestinal tone or both.

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Review

Circulation and Metabolism of the Human Brain in Health and Disease*

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ONE important approach to the enigma of the human brain resides in a study of its circulation. A number of diseases produce serious cerebral manifestations and sometimes death by interference with the circulatory nutrition of the brain. Others are associated with a breakdown at some point or other in the complex series of metabolic processes which underlie normal cerebral activity. Measurement of the cerebral blood flow in man may afford not only some insight into these circulatory disturbances but also an opportunity to investigate the more abstruse problem of cerebral metabolism. Such studies are yet in their infancy and, compared to what is yet to be learned, our accumulated knowledge is modest indeed. From this point of view a summary of our knowledge at this time is warranted, if only to point out the great gaps which still exist.

CEREBRAL CIRCULATION

Experiments in lower animals,[4,42] have contributed a wealth of information upon the fundamental physiology of the cerebral circulation but knowledge of its status in clinical disease depends upon studies in man. By examination of retinal vessels,[3] oxygen contents of internal jugular and arterial blood,[35,53] or by employing thermoelectric,[8] spinal fluid displacement[5] or dye-injection technics[11] some insight into the human cerebral circulation has been acquired. More recently the nitrous oxide method[22,29,30] has made more or less quantitative information clinically available. By means of this technic, which depends upon the rate of loss of an inert gas from the blood passing through the brain, a normal value has been obtained for human cerebral blood flow of 54 cc. per 100 gm. of brain per minute, corresponding to a value of 740 cc. per minute for a brain of average weight. The oxygen consumption of the normal human brain is found by the same method to equal 3.3 cc. of oxygen per 100 gm. of brain per minute, or a value of 46 cc. per minute for the whole organ. Thus the brain, representing 2 per cent of the body weight, normally receives about one-sixth of the heart's output of blood and consumes nearly 20 per cent of the oxygen utilized by the body as a whole.

Anatomy of Cerebral Circulation. In man the brain is supplied with blood entirely by means of the paired internal carotid and vertebral arteries. There are no significant anastomoses with the extracerebral arteries such as exist in lower mammals. In general the internal carotid arteries supply the anterior and middle portions of the brain on each side while the single basilar artery formed by the union of the two vertebrals supplies the occipital lobes, portions of the temporal lobes and the structures in the posterior fossa. These three main sources communicate with each other at the base of the brain in the so-called circle of Willis, the two carotids by means of the anterior communicating artery and each carotid with the basilar by way of the posterior communicating arteries. Under normal

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circumstances, however, the pressure in these three mainstems is equal, with the result that there is little exchange of blood among them.[46] Only when occlusion of one or the other occurs does the circle of Willis assume functional importance. Because these anastomoses are not completely adequate, acute occlusion of one carotid significantly lowers the pressure beyond the point of block[50] and therapeutically offers a means of lessening the strain upon aneurysms along that distribution, or of partially reducing the effects of an arteriovenous communication. Although the inadequacy of the circle of Willis is the basis for therapeutic benefit in such cases, it is also the factor responsible for a fairly high incidence of serious complications following unilateral carotid ligation[38] especially in elderly individuals, such sequelae being undoubtedly the result of a severe reduction in blood flow to the region involved.

In contrast to the arterial supply the drainage of blood from the brain is achieved by a large number of freely communicating channels so that occlusion of one or the other causes relatively little circulatory embarrassment. Blood leaves the brain by way of the internal jugular veins, by means of numerous emissary channels between the dural sinuses and the extracranial venous system[46] and by way of the large spinal venous plexus which arises from the cavernous and petrosal sinuses and communicates segmentally with the thoracic and abdominal veins.[1] This plexus, often overlooked, is apparently capable of handling the entire cerebral venous drainage, since occlusion of both jugulars and even thrombosis of the superior vena cava are accompanied by surprisingly few cerebral symptoms.[1]

Physiology, Normal and Pathologic. The rate of cerebral blood flow, like that of the circulation through any organ, depends upon only two factors although each of these may in turn be the resultant of a host of other variables. These two factors are (1) the pressure head or the difference between the arterial and venous pressures at the level of the cranium and (2) the resistance or hindrance imposed on the flow of blood through the vessels of the brain.

1. *Blood Pressure Head:* This is largely determined by the mean arterial blood pressure although conditions such as congestive heart failure in which there is a generalized rise in venous pressure may involve a reduction in pressure head and blood flow on that basis. Such measurements in congestive heart failure have not yet been reported. Recent investigation does not substantiate the earlier belief that cerebral blood flow passively follows changes in arterial blood pressure. Studies in intact human beings have strengthened the concept that a normal arterial blood pressure is zealously maintained by numerous homeostatic mechanisms such as the carotid sinus reflex and central control of peripheral vascular tone; and that as long as the mean arterial blood pressure remains above a critical minimum level, cerebral blood flow is actually regulated intrinsically by changes in cerebrovascular resistance. The critical level of blood pressure below which cerebral circulation is inevitably reduced has not yet been quantitatively estimated, although the cerebral symptoms associated with *orthostatic hypotension* suggest that it is not far below the normal mean pressure. The syncope accompanying the *carotid sinus syndrome*, *Stokes-Adams syndrome* and the ordinary *fainting spell*, as well as the more prolonged cerebral derangements resulting from *hemorrhagic* or *traumatic shock* are probably examples of cerebral circulatory insufficiency on a basis of inadequate arterial blood pressure.

2. *Cerebrovascular Resistance:* Reference has already been made to this important factor as the predominant regulator of cerebral blood flow at blood pressures above the shock level. Cerebrovascular resistance is measured in units of pressure head necessary to cause a unit flow of blood through the brain, the average normal value being 1.6 mm. Hg per cc. of blood per 100 gm. of brain per minute. It represents the resultant of all factors tending to impede the flow of blood through the brain and includes intracranial pressure, blood viscosity and organic

changes in as well as the functional tone of cerebral vessels.

Intracranial pressure: The thin walled vessels of the brain, immersed in cerebrospinal fluid, accurately reflect changes in pressure within that medium. When the intracranial pressure rises, as it does for example in *space-taking lesions of the brain*, these vessels are compressed and the cerebrovascular resistance increases to a comparable degree.[33] This should result in a proportionate reduction in cerebral blood flow except that the rise in blood pressure which accompanies increased intracranial pressure tends partially to compensate for the increased resistance and to preserve a normal blood flow. With excessive increases in cerebrospinal fluid pressure, however, to levels above 400 mm. of water (Table 1) the rise in blood pressure is inadequate and a significant cerebral circulatory insufficiency results.

TABLE 1

PHYSIOLOGIC AND PATHOLOGIC STATES INVOLVING ALTERATIONS IN CEREBROVASCULAR RESISTANCE AND BLOOD FLOW

Condition	Mean Arterial Blood Pressure mm. Hg	Cerebral Blood Flow	Cerebral O_2 Consumption	Cerebrovascular Resistance
		cc./100 gm./min.		mm. Hg/cc./100 gm./min.
Normal[31]	85	54	3.3	1.6
Hyperventilation[32]	98	34	3.7	2.9
CO_2 (5–7%)[32]	93	93	3.3	1.1
O_2 (85–100%)[32]	98	45	3.2	2.2
O_2 (10%)[32]	78	73	3.2	1.1
Increased intracranial pressure[33]	118	34	2.8	3.5
Primary polycythemia[23]	108	25	3.0	4.3
Anemia[23]	78	79	3.3	1.0
Cerebral arteriosclerosis[6]	121	41	2.8	3.0
Cerebral hemangioma[48]	75	164	3.3	0.5
Essential hypertension[25]	159	54	3.4	3.0

On the other hand, the cerebrospinal fluid serves a most important function in the circulatory homeostasis of the brain. Since the only important distensibility of the cranial cavity and its contents lies in its veins and since these are in direct communication with the great veins of the body, the cerebrospinal fluid becomes, from the point of view of hydraulics, a part of the venous system of the body and instantaneously reflects venous pressure changes. Thus a cough, a sneeze, or a straining of the thoracic and abdominal muscles, which cause an immediate rise in arterial and venous pressure at the head, cause a parallel increase in intracranial pressure with the result that there is no net change in cerebral hemodynamics and the intracapillary pressure rise, which might have been sufficient to burst these thin walls, is effectively neutralized by the increased pressure around them.[15] Men exposed to a *centrifugal force* several times that of gravity may retain consciousness and suffer no serious reduction in cerebral blood flow even though the mean arterial blood pressure at head level is nearly zero.[17] This paradoxical phenomenon is explained by a comparable reduction in venous pressure at the head so that the arteriovenous pressure difference is preserved. Under such circumstances the cerebral capillaries, which would ordinarily collapse as a result of the very low pressures within them, are prevented from doing so by the cerebrospinal fluid which at head level suffers the same reduction in pressure as do the cerebral vessels. The capillaries of the face and ear, which are without such support, collapse under the same conditions and become

bloodless. In addition to maintaining patency of cerebral vessels, the low intracranial pressure removes a fraction of the cerebrovascular resistance and thereby helps to sustain the cerebral circulation. These functions of the cerebrospinal fluid system dramatically demonstrated during positive acceleration may also operate in the assumption of the *upright posture* under normal circumstances to prevent a significant reduction in cerebral blood flow.[47]

Blood viscosity: Although relatively constant under most conditions, the viscosity of the blood, largely dependent on the proportion of erythrocytes, may vary widely from the normal in *anemia* and *polycythemia*. Since a viscous fluid offers more frictional resistance in its flow through narrow tubes, marked changes in viscosity will be reflected in alterations in cerebrovascular resistance. In severe anemias of all types there is a reduction in this resistance and a corresponding increase in cerebral blood flow;[32,41] this acts as a compensatory mechanism tending to maintain a normal state of oxygen delivery. Conversely, in polycythemia vera there may be a threefold increase in blood viscosity and a corresponding increase in cerebrovascular resistance. Indeed, we have observed in this condition a cerebral blood flow of 22 cc. per 100 gm. of brain per minute, the lowest value recorded in any living patient. Because of the high oxygen concentration of this blood and since the CO_2 carrying capacity is closely related to the hemoglobin content, such patients are able to maintain in their brains normal exchanges of these two gases in spite of the severe reduction in blood flow.[23]

Organic change in cerebral vessels: Examination of the brains of patients who have suffered from the senile psychoses usually reveals marked sclerosis and narrowing of the lumen of cerebral arteries and a good deal of parenchymal atrophy. It has usually been assumed that *cerebral arteriosclerosis* imposes a resistance to the flow of blood through the brain and that the resultant decrease in nutrition has led to the functional and anatomic changes in the brain substance. Recent observations in senile psychotic individuals made during life have strengthened that theory.[6] The cerebrovascular resistance was found to be significantly increased with a resultant decrease in cerebral circulation. Probably on that basis the oxygen consumption of the brain was found to be depressed with resultant mental aberration. *Meningovascular syphilis* has also been found to be associated with a decreased blood flow on the basis of an augmented vascular resistance in the brain,[37] a clinical confirmation of the vascular changes seen in such brains at necropsy.

Within the category of organic vascular change may be placed those anomalies characterized by large arteriovenous communications. In measurements obtained in patients with *cerebral hemangiomas*[48] cerebrovascular resistance was found to be greatly reduced by these abnormal shunts and blood flow to the brain tremendously accelerated although cerebral metabolism was not perceptibly disturbed. Since the circulation through these shunts exceeded a liter per minute, a considerable strain was thrown upon the heart, demonstrated by measurable increase in cardiac output and by cardiac enlargement.

Cerebrovascular tone: In this function resides the fundamental regulation of cerebral nutrition in most normal and pathologic states. By constriction or dilation of the flood gates of the cerebral circulation either locally or generally, a remarkable degree of homeostasis is maintained in all but the most abnormal circumstances. Alterations in cerebrovascular tone may be achieved by certain neurogenic mechanisms, by humoral agents or by a number of drugs.

The *neurogenic control* of the cerebral circulation is still only poorly defined. The sympathetic innervation to cerebral vessels originates in the thoraco-lumbar outflow and ascends via the cerevical sympathetic chains traversing the stellate ganglion. There is also anatomic evidence[2] for vasodilator fibers originating in the medulla and traversing the facial and greater super-

ficial petrosal nerve. Granting the existence of such cerebrovascular innervations, one finds the evidence for their exact functions vague and equivocal. In anesthetized animals stimulation of the cervical sympathetic chain may produce evidence of mild cerebral vasoconstriction[42] although this is not common to all species or preparations. Evidence for a normal tonic constrictor effect from the cervical sympathetics was not found in man[16] in whom bilateral procaine block of the stellate ganglia, although followed by signs of sympathetic paralysis in the face and eyes, produced no change in cerebrovascular resistance or blood flow. It is, of course, perfectly possible that reflex cerebrovascular spasm in response to embolism or thrombosis may occur and be mediated by this sympathetic innervation. Indeed, such a possibility must be entertained in order to explain the beneficial effects reported by some[12] in these conditions after stellate ganglion block. In some patients suffering from postencephalitic Parkinsonism surgical removal of both stellate ganglia has been followed by a significant increase in cerebral blood flow.[49]

A plausible neurogenic mechanism which requires experimental demonstration in man is a cerebrovascular regulation by way of the carotid sinus. This could offer a means of maintaining the cerebral circulation at a normal level in the face of marked alterations in arterial blood pressure at the head level. One bit of clinical evidence for such a reflex is to be found in that type of hyperactive carotid sinus syndrome in which syncope occurs without a bradycardia or fall in blood pressure.[52] An explanation which has been advanced is that stimulation of the sinus produces intense cerebral vasoconstriction in these individuals, an exaggeration of the normal response.

In contrast to the neurogenic control *chemical substances* exert striking and well recognized effects upon cerebrovascular tone. A large number of experiments on lower animals have demonstrated the ability of *carbon dioxide* to dilate cerebral vessels. Recently quantitative measurements performed in normal young men have resulted in the conclusion that increases in blood carbon dioxide tension achieved by breathing this gas in 5 to 7 per cent concentration result in a great acceleration of cerebral blood flow averaging 75 per cent above the normal value.[32] This increased flow is the result of a decrease in cerebrovascular resistance. (Table 1.) Clinical application of such concentrations of carbon dioxide is to be found in anesthesiology in which recovery from ether anesthesia may be hastened not only by the respiratory stimulation produced but also by the accelerated cerebral blood flow which hastens the removal of the anesthetic from the brain. The addition of carbon dioxide to inspired gas will also enable an individual to tolerate extremely low oxygen tensions.[9] Conversely, a decrease in blood carbon dioxide tension produced by moderate hyperventilation was followed by a marked constriction of cerebral blood vessels and a reduction in blood flow by approximately one-third.[30] As a result of this a definite degree of cerebral anoxia could be demonstrated, the cerebral venous oxygen saturation falling from a normal value of 63 per cent to a mean of 43 per cent. The derangements in and loss of consciousness which accompanies clinical hyperventilation can be explained on the basis of cerebrovascular constriction and cerebral anoxia.

A factor probably of equal or greater importance and difficult to separate from carbon dioxide tension is the *hydrogen ion concentration*. In the studies cited above the inhalation of 5 to 7 per cent carbon dioxide produced a mild acidosis (arterial pH of 7.33) while hyperventilation was associated with a fairly severe alkalosis (arterial pH of 7.54) so that the effects of CO_2 on cerebrovascular tone may well be entirely those of the hydrogen ion. In fact, equally good correlations are obtained between cerebral blood flow and either arterial pH or carbon dioxide tension.[32] In at least one clinical condition (diabetic coma) in which there is an increased hydrogen ion concentration in the blood but a markedly reduced carbon

dioxide tension, there is still a good deal of cerebral vasodilation[28] so that in this type of acidosis there is an ample cerebral circulation often in spite of peripheral circulatory collapse.

Oxygen tension is another important factor in the regulation of cerebrovascular resistance. The breathing of a mixture containing 10 per cent oxygen produces a marked increase in cerebral blood flow even though the blood pressure falls somewhat.[32] The cerebral vasodilation produced by this low-oxygen mixture is equal to that following 5 to 7 per cent CO_2 inhalation and occurs in spite of a significant decrease in arterial CO_2 tension brought about by anoxic hyperpnea. It must therefore be concluded that anoxia has as powerful a dilator action on cerebral vessels as therapeutic concentrations of carbon dioxide. In asphyxia in which both factors are operating in the same direction, one would expect a marked increase in cerebral blood flow. This is found to be the case in severe pulmonary disease in which serious anoxemia and hypercapnia converge to cause a more than two-fold increase in cerebral circulation.[23] Tensions of oxygen above that of room air appear to cause a slight constriction of cerebral vessels. The inhalation of 85 to 100 per cent oxygen is associated with a 13 per cent decrease in cerebral blood flow on the basis of a moderate increase in cerebrovascular resistance.[32] This is probably not a sufficient restriction of cerebral circulation to constitute any contraindication to the use of oxygen therapy.

A most important aspect of cerebral hemostasis consists in an adjustment of circulation to *local metabolic needs*. That such an adjustment does occur is indicated by the findings of a marked increase in cerebral blood flow which parallels the rise in cerebral metabolism during a metrazol convulsion[43] and in general by a correlation between blood flow and metabolic activity in the brain. By means of thermoelectric measurements of blood flow, illumination of the eye has been shown to be associated with an increase in circulation locally in the occipital cortex in anesthetized cats.[42] In a patient with a cranial defect over a hemangioma of the occipital lobe an increased circulatory bruit has been detected by means of a sensitive microphone during acts of visual concentration.[7] The mechanism whereby this adjustment is accomplished has not been definitely elucidated but the fact that at least three products of metabolism (decrease in oxygen tension, increase in hydrogen ion concentration and in carbon dioxide tension) are dilators to cerebral vessels suggests these substances as possible agents. Thus a portion of the brain may be called to greater activity by some stimulation. This increased activity produces a local increase in acidity and carbon dioxide tension and a lowered oxygen tension within the tissue. In response to these and perhaps other changes the blood vessels passing through this tissue dilate, permit a greater volume of blood to flow, increasing the supply of oxygen and the removal of metabolic products, and in this way a nice constancy of the cellular environment is maintained.

In addition to those endogenous substances there are numerous *drugs* which presumably affect cerebrovascular tone. The experimental evidence in some cases, however, is fairly indirect. On the basis of a large number of experiments in animals and man by different groups cerebral vasodilator properties have been ascribed to nitroglycerine, acetylcholine, histamine, alcohol, caffeine, ether and papaverine. On the other hand, cerebral vasoconstriction may under certain experimental circumstances be produced by epinephrine, caffeine, ergotamine and posterior pituitary extract. Since in the animal experiments the dosages employed and the routes of administration were far removed from clinical usage, and in the studies in man cerebral blood flow was often measured by methods of questionable veracity, it is fair to state that the effects of drugs in therapeutic dosage on the human cerebral circulation are largely undetermined. Recently *histamine* has been shown consistently to dilate the cerebral

vessels in man although because of its tendency to reduce the blood pressure it does not always significantly increase cerebral blood flow.[44] *Aminophylline* administered intravenously in therapeutic dosage produces a constant constriction of cerebral vessels, a significant reduction in cerebral blood flow and a resultant cerebral anoxia.[51] *Dihydroergocornine*, a derivative of one of the ergot alkaloids, has been shown to cause a release of cerebrovascular resistance in patients with essential hypertension and, to a lesser extent, in normal subjects.[14] With these few exceptions the clinical pharmacology of the cerebral circulation remains to be explored.

There are a few clinical diseases in which there is a characteristic increase in cerebrovascular tone the mechanism of which is still obscure. *Essential hypertension* is associated with a high cerebrovascular resistance which in some cases may be more than double the normal value.[26] Cerebral blood flow, however, remains normal since the increased resistance parallels the increase in mean arterial blood pressure. A number of possibilities present themselves by which to explain this inordinately high tone of cerebral vessels and the hypertension. The increased resistance may be primary and the hypertension a compensatory adjustment brought about by cerebral anoxia. This is unlikely since there is no evidence of a restricted cerebral circulation in essential hypertension, whereas in other conditions, such as high intracranial pressure or cerebral arteriosclerosis in which the hypertension is probably compensatory, some degree of cerebral ischemia exists to initiate and maintain this mechanism. A second possibility is that the increased cerebrovascular tone is a homeostatic response on the part of these vessels to a hypertension originating elsewhere, a response which serves to prevent an excessive cerebral blood flow. If this were the case, a sudden fall in blood pressure in hypertensive patients to normal levels should be promptly followed by a comparable relaxation of cerebral blood vessels and the maintenance of a normal blood flow through the brain. When by differentially blocking the sympathetic innervation to the lower part of the body in hypertensives such a fall in blood pressure is achieved, there is not an immediate and complete relaxation of cerebral vessels with the result that cerebral blood flow is significantly decreased and some degree of cerebral anoxia is acutely produced.[26] On the basis of these considerations it appears that the increased cerebrovascular resistance in essential hypertension is neither primary nor secondary in the brain but rather a reflection of a uniform increase in vascular tone throughout the body. The uniformity and generalized nature of this constriction, its involvement of cerebral vascular beds where sympathetic tone is demonstrably weak and the failure of blockage of the known sympathetic innervation to the head to alter it[16] all suggest some humoral agent as its mediator.

Although an acute fall in blood pressure obtained by differential spinal anesthesia causes some embarrassment of cerebral circulation, that produced by an adrenolytic and sympatholytic agent, dihydroergocornine, causes no demonstrable reduction in cerebral circulation and what appears to be a greater degree of cerebrovascular relaxation.[14] Likewise a persistent fall in blood pressure as a result of lumbodorsal sympathectomy is associated with some compensatory phenomena such that cerebral blood flow remains normal.[45] In addition to essential hypertension there are some other diseases which appear to be associated with an increase in cerebrovascular tone. Measurements have been made in *eclampsia* and *preeclamptic states* of pregnancy which demonstrate an increased cerebrovascular resistance in these conditions, but because of associated hypertension cerebral blood flow is maintained at normal or nearly normal values.[36] The similarity of these phenomena to those observed in essential hypertension is apparent. It is probable that acute glomerulonephritis may show comparable changes although such

studies in this disease have not yet been reported.

Few studies have, to the present time, been made in the various encephalopathies associated with aggravated states of hypertension, eclampsia and glomerulonephritis. Those which have been done[23,36] indicate actual impairment of the cerebral circulation of fair magnitude. Whether this in itself may explain the mental and neurologic disturbances in these diseases is not clear; indeed, the entire question of the occurrence of cerebrovascular spasm to a degree sufficient to embarrass the cerebral circulation is a problem which requires much further investigation.

METABOLISM OF THE LIVING HUMAN BRAIN

At present it is well established that glucose is by far the predominant foodstuff of the brain. Accurate analyses of arterial and cerebral venous blood of normal man[10,31] have yielded a cerebral respiratory quotient which is practically unity (0.99) and compatible with the exclusive burning of carbohydrate. Furthermore, examination of the glucose, oxygen and lactic acid contents of these bloods have demonstrated[10] that practically all of the oxygen consumed by the brain is utilized in the complete oxidation of glucose with an extremely small portion of the glucose going to lactic acid by anaerobic metabolism. It appears that the glucose is not directly burned but rather, by an anaerobic breakdown, is converted to intermediary products which are then efficiently oxidized in the Krebs cycle.

The energy thus derived is not immediately used by the neurones but is stored in the cells as high energy phosphate compounds, such as phospho-creatine and adenosine triphosphate, to be released upon demand. Although some cells are able to utilize energy released in the anaerobic breakdown of glucose, the brain is unable to sustain its complex function in this way and is completely dependent upon oxidative energy and therefore upon a continuous supply of oxygen. Since the brain cannot or at least does not appear to utilize fats or protein for energy, a continuous supply of glucose is equally essential to normal brain activity.

Cerebral Metabolism and Mental State. Although the relationship between the mind and the brain has been the subject of philosophic controversy for many centuries, and despite a recent tendency among some schools of psychiatry to divorce one from the other, there is little doubt that the two are intimately associated. Stop the flow of blood to the brain for a few seconds, or add to that blood a small amount of an anesthetic drug and profound changes are reflected in the mind. Recent studies have shown a remarkable correlation between mental function and cerebral metabolism. The latter can be evaluated in man in terms of oxygen consumed per 100 gm. of brain per minute. In *conscious and alert* individuals this value has a mean of 3.3 cc. of oxygen / 100 gm. /min.[31] In patients who, as a result of acidosis, increased intracranial pressure or hypoglycemia, are *conscious but confused* this value falls to a mean of 2.6, while in patients who are *comatose* from whatever cause one finds a marked depression in cerebral metabolism with a mean value of 2.0 cc /100 gm. /min., a 40 per cent reduction from the normal figure. These results indicate that states in which there is a generalized reduction in cerebral metabolism are associated with changes in consciousness although it does not necessarily follow that changes in the mental state may not occur as a result of highly localized metabolic changes in small specialized areas which do not affect the overall oxygen consumption obtained by this method. In *schizophrenia*, including the far advanced stages, oxygen consumption by the brain as a whole is exactly normal.[34] Moreover, during *pentothal semi-narcosis* which was usually associated with considerable mental improvement, there was no detectable change in cerebral oxygen utilization. Cerebral metabolism during sleep and during mental effort has not yet been determined. A state of *anxiety or apprehension* may be associated with a greatly augmented

oxygen consumption by the brain. In one subject who had yielded previous resting values of 3.4, 3.9, 3.2 and 4.2 cc. O_2/100 gm./min., a value of 5.0 was obtained during a state of grave apprehensiveness.[23] Studies of cerebral oxygen consumption during *convulsions* have not been made in man; they may certainly be expected to show the same, practically two-fold, increase observed in the monkey.[43] (Table II.)

TABLE II

CONDITIONS INVOLVING ALTERATIONS IN MENTAL STATE OR CEREBRAL METABOLISM

Condition	Mental State	Mean Blood Pressure mm. Hg	Cerebral Blood Flow	Cerebral O_2 Consumption	Cerebrovascular Resistance mm. Hg/cc./100 gm./min.
			cc./100 gm./min.		
Normal[31]	Alert	85	54	3.3	1.6
Schizophrenics[34]	Alert-inaccessible	95	54	3.3	1.7
Schizophrenics, narcosynthesis[34]	Alert-more accessible	95	54	3.3	1.8
Cerebral arteriosclerosis[6]	Confused	121	41	2.8	3.0
Diabetic acidosis[28]	Confused	86	45	2.7	2.1
Insulin hypoglycemia[27]	Confused	86	61	2.6	1.4
Brain tumor[33]	Comatose	122	34	2.5	3.6
Pentothal anesthesia[24]	Comatose	78	60	2.1	1.3
Insulin coma[27]	Comatose	93	63	1.9	1.5
Diabetic coma[28]	Comatose	66	65	1.7	1.1

Mechanisms Responsible for Central Nervous System Depression. On the thesis that normal cerebral metabolism and therefore central nervous function depends on an optimal concentration of certain nutrients and metabolic products about the neurone and the presence within it of properly functioning mechanisms for the conversion of energy, it is possible to outline possible defects leading to decreased function.

1. *Deficit of essential nutrients in arterial blood:* Although a host of substances are undoubtedly essential to the growth, repair and delicate adjustment of cerebral structure and function, only two—oxygen and glucose—appear to provide the energy constantly required for this activity. Deficits in these two substances are incompatible with continued survival for more than a few minutes in the case of oxygen and a few hours in the case of glucose. This difference in survival times does not imply that oxygen is more critical than glucose to cerebral function; it merely reflects the greater storage capacity of the brain for carbohydrate. Rough calculation reveals that the blood within the brain at any one time contains a total of 5 cc. of oxygen while not more than 2 cc. of oxygen are dissolved in the brain substance itself. At a normal rate of oxygen utilization of 46 cc./minute this total of 7 cc. would last about ten seconds, and symptoms of anoxia would appear before it was entirely consumed.

If the *anoxia* be slowly progressive, there will be sufficient time to observe its biochemical effects in the brain. When the arterial oxygen saturation falls below 50 per cent of the normal, a progressive increase in lactic acid in the brain occurs, a reflection of a shift toward anaerobic breakdown of glucose.[13] Above that degree of hypoxia there are subtle changes in mental function but no measurable decrease in cerebral oxygen consumption.[32] Although the anaerobic metabolism of glucose may explain the greater resistance of the newborn to anoxia,[18] this source of energy is not usually adequate for as the anoxia progresses there occurs a rapid depletion of phosphocreatine, a high energy phosphate molecule, in the brain,[13] reflecting

the lack of oxidative energy necessary for its synthesis. When these high energy stores are depleted, central nervous function stops. Clinical states of central nervous depression attributable to arterial anoxemia are of course severe *pulmonary disease*, severe *anemias*, *carbon monoxide poisoning*, *asphyxia* and exposure to *high altitudes*.

There are appreciable stores of glucose and glycogen, which is readily convertible to glucose, within the living brain probably amounting to 2 gm. of glucose or its equivalent[21] in the case of the whole human brain. These stores render the cerebral effects of severe hypoglycemia much less acute than those of anoxia. In studies upon schizophrenics receiving *insulin shock* therapy there was a progressive decrease in the utilization of oxygen and glucose by the brain as the arterial blood glucose level fell from a normal fasting value to an average of 8 mg. per cent in deep coma.[27] In this state cerebral oxygen consumption was reduced to 50 per cent of the normal figure while the utilization of glucose from the blood was practically negligible. Since the cerebral respiratory quotient was still unity, it is probable that in this stage the low grade of metabolism is maintained by the utilization of the glycogen stored in the brain, which stores have been shown to be depleted following insulin hypoglycemia.[21] It may be calculated that the glycogen of the brain will support cerebral metabolism for about ninety minutes at the low level present in coma. This period is roughly equivalent to the time in which a patient may remain in deep hypoglycemic coma without irreversible damage to the brain. It is probable, therefore, that after the glycogen stores are depleted the hungry enzyme systems turn to structural components of the neurone, restoration of which, after recovery, is more difficult than replacement of glycogen.

2. *Restriction of cerebral circulation:* Even though the arterial blood may be adequately oxygenated and contain normal amounts of glucose, an impairment of cerebral circulation may prevent adequate quantities of these substances from reaching the brain. This circulatory impairment may be chronic as in cerebral arteriosclerosis, or acute and profound as in ventricular asystole. Because of the storage of carbohydrate in the brain the effects of a sudden cessation of cerebral circulation are largely those of anoxia aggravated to some extent by the accumulation of carbon dioxide and hydrogen ion. Acute arrest of the cerebral circulation for periods up to 100 seconds has been experimentally produced in man by means of an inflatable rubber cuff placed about the neck, occluding both carotids and probably also the vertebrals in the lower part of their course.[40] The effects produced are similar to those of profound anoxia. After about five seconds of occlusion the eyeballs became fixed in the midline. One second later consciousness was lost and the eyeballs turned upward. Before loss of consciousness many subjects experienced narrowing of the visual fields, blurring and graying of vision, then complete loss of vision although sounds could still be heard. Following the period of unconsciousness there were mild tonic and clonic convulsions. Some subjects reported various paresthesias of the arms and legs during the arrest of the cerebral circulation. Mental changes such as excitement, euphoria or confusion frequently preceded the unconsciousness or followed release of the occlusion. When circulatory arrest was prolonged, cyanosis, involuntary urination and defecation, bradycardia, dilation of the pupils, disappearance of corneal and abdominal reflexes and the appearance of certain pathologic reflexes were noted. The electroencephalogram exhibited large slow waves which corresponded closely in onset to the unconsciousness.

There were no residual effects from arrest of the cerebral circulation for periods up to 100 seconds; consciousness was regained in fifteen or twenty seconds following restoration of the circulation and within two minutes the subjects were able to walk from the room. From observations during ventricular asystole it appears that complete arrest

of the cerebral circulation for more than four or five minutes is incompatible with complete recovery of central nervous function. Some or all of these effects of acute reduction in cerebral blood flow are seen clinically in the *Stokes-Adams syndrome*, in *orthostatic hypotension*, the *carotid sinus syndrome* and in the common *faint*.

When there is a chronic restriction of the cerebral circulation below a minimal level, interference with cerebral metabolism takes place and associated mental derangements appear. The reduced cerebral circulation seen in *cerebral arteriosclerosis* is associated with cerebral anoxia, a significant reduction in cerebral oxygen consumption and, probably on that basis, disturbances in psychic function.[6] In diseases associated with high *intracranial pressure* the restriction in blood flow through the brain may be sufficient to produce serious defects in metabolism associated with confusion or coma.[33]

3. *Intracellular defects in metabolism:* In many conditions cerebral metabolism and function are disturbed even though adequate amounts of oxygen and glucose surround the nerve cells. These disturbances must be attributed to defects in the complicated intracellular mechanisms whereby glucose and oxygen are altered, then combined, and the resultant energy transferred to functional activity. These intracellular defects may be primary or they may occur as a sequel to one of the two factors already discussed. Thus prolonged ischemia, anoxia or hypoglycemia may produce less readily reversible intracellular defects so that what started as an extracellular disturbance readily corrected by artificial respiration, the administration of glucose or raising the blood pressure now becomes a grave impairment of intracellular enzyme systems which is called irreversible because its nature is still unknown. Barcroft put this succinctly in his classic statement that anoxia not only stops the machine but also wrecks the machinery. In the brain hypoglycemia acts in a similar fashion.

The intracellular defects in metabolism may consist either of actual deficiencies within important enzyme systems or the presence somewhere of undesirable substances which inhibit or depress these systems. It is not always easy to distinguish between the two and it is therefore difficult to characterize each clinical state as belonging to one or the other category.

There are a number of *congenital metabolic defects* such as mongolian idiocy, cretinism or phenylpyruvic oligophrenia in which presumptive evidence for a decreased oxygen utilization has been found[19] related probably to specific intracellular deficiencies. Certain types of *avitaminosis* especially those of the B complex (e.g., pellagra, Wernicke syndrome) are associated with mental disturbances quite possibly on the basis of cerebral deficits of these substances known to be important in carbohydrate metabolism.

In *post-convulsive states*, the "irreversible" stages of *anoxia* and *hypoglycemia* and in *diabetic coma* there may be an exhaustion of high energy phosphorus compounds in the neurones. In the case of diabetic coma recent work showing an effect of insulin catalyzing the transfer of oxidative energy to the high energy phosphate bond[39] suggests this as a real possibility.

Cerebral metabolism may be deranged by the presence of *depressant agents* of endogenous or exogenous origin. Among those originating within the body are the *hydrogen ion* and the products which accumulate in *uremia* and *ketosis*. In diabetic acidosis and coma the confusion and unconsciousness are well correlated with a considerable depression in cerebral oxygen consumption.[28] This is not on the basis of inadequate supply to the cells of the brain since a normal or augmented cerebral circulation carrying adequate quantities of oxygen and glucose is maintained in this condition. The defect is probably intracellular and may be due to the acidosis or ketosis *per se*. The metabolism of brain tissue slices is quite sensitive to pH changes and the metabolic depression in diabetic acidosis does show some correlation with arterial pH. A better correlation, however, is found with blood ketone con-

centrations; and since at least one of these substances (acetoacetate) is capable of causing coma in itself when injected into animals, it seems reasonable to suppose that much of the coma and depressed cerebral metabolism in this condition is due to their presence in excessive amounts. The nature of the cerebral depression underlying uremic coma requires more investigation.

A number of drugs and poisons produce central nervous depression by intracellular block of vital enzyme systems. A classical example is the *cyanide* ion which, by firmly binding cytochrome oxidase, prevents the reversible oxidation and reduction of this system essential to the chain of reactions whereby molecular oxygen oxidizes its various substrates. A more practical and clinically useful example is to be found in the action of the various *anesthetic drugs*. During pentothal or ether anesthesia in man there is a 40 per cent decrease in cerebral oxygen utilization even though cerebral blood flow and arterial contents of oxygen and glucose are adequate.[20,24] The exact site of this metabolic depression is not as yet well defined; it differs from the others in being sustained but not necessarily progressive and, in contrast to anoxia or hypoglycemia, readily reversible. It is this peculiar reversibility of the effects of narcotics on cerebral metabolism which permits their widespread usefulness.

Because of the tremendous complexity of the human brain it is not surprising that present knowledge of its metabolism is fragmentary and quite incomplete. Further information, however, requires only the desire to obtain it and the conviction that somehow an understanding of the brain may yield some little insight into the mysteries of the mind.

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Seminars on Cancer Research

Genetic Aspect of Cancer Research*

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With the acquisition of more experimental data it is becoming quite evident why the fundamental nature of cancer is not more understandable. The improvement in technic has perhaps made it possible to obtain answers to many problems that were thought to be beyond our vision only a few years ago but replacing these are other and even more complex questions that must await the development of more fundamental assays before they may be solved. This does not necessarily imply, however, that the cancer problem, as is the case in other diseases, may not be controlled before the basic details are entirely comprehended.

In discussing the various genetic aspects of cancer research one might become involved in many fundamental issues, each with different implications upon the problem as a whole. The experimental data to be considered in this report will therefore be limited to those obtained in mice of various inbred stocks, in which is possible "to hold genetics constant while we alter other factors such as hormonal level or other chemical or physiological variables. We can then hold these factors constant and by altering the genetic constitution obtain a vastly clearer picture of the relative role of not only each broad general field of agents but of the particular part played by individual components within these fields."[54] With such homozygous material one should obtain definite evidence for the action of genes in the development of various types of tumors and perhaps determine the number involved.

The genetic basis for the transplantation of both normal and neoplastic tissues has been reviewed during the past few years by several writers[53,56] and the experimental induction of cancer by carcinogens will be considered in another paper in this series. While there is little doubt of the role of the genetic constitution of the host in induced carcinogenesis, the recent work of Kirschbaum[45] who compared the action of various agents in the induction of leukemia in mice might be recalled. He wrote: "In general, it might be concluded that various agents are effective in inducing leukemia or in accelerating its onset depending on the genetic constitution of the mice used for experimentation. Because a strain of mice is susceptible to the action of one such agent does not imply necessarily that the animals are susceptible to another agent which has been shown to be leukemogenic for still another strain. The problem of leukemogenesis in mice is very complex. First, multiple agents can induce leukemia. Second, mice of only certain genetic constitution are susceptible to only certain agents. Third, genetic susceptibility to one agent, or to the spontaneous disease, cannot necessarily be correlated with susceptibility to other leukemogenic agents. Fourth, synergists condition the response to carcinogens; synergists vary in their effectiveness with the strain of animal involved."

GENETICS OF MOUSE LEUKEMIA

MacDowell and Richter[61] were among the first investigators to employ inbred

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strains for experimental work on the genesis of leukemia in mice. From the results of reciprocal crosses between a high (C_{58}) and a low (StoLi) strain they reported that while the predisposition to the disease was specifically inherited, the somatic expression of leukemia in mice of the segregating generations did not disclose definite genetic ratios. Some suggestion of a maternal influence was indicated because the hybrids descended from maternal parents of the cancerous stock showed a higher incidence than did the mice derived by reciprocal matings. Foster nursing failed to reveal any milk influence.

Although Mercier[63] concluded that the genetic susceptibility for spontaneous leukemia could be accounted for upon the basis of a simple recessive, other workers were finding approximately the same incidence in the F_1 hybrids as in mice of the high cancerous stocks, showing the action of dominant genes. Cole and Furth[28] reported that while the genetic susceptibility may vary for different stocks, the cross between the Ak and Rf strains gave evidence that multiple factors were involved as well as undetermined environmental factors. In this and another cross in which the same leukemic strain was used[33] a maternal influence was indicated. Kirschbaum and Strong[47] and Kirschbaum[44] used the inbred F strain as their high leukemic line and when it was crossed to mice of three low strains, by reciprocal matings, the incidences in the F_1 hybrids were approximately the same as was observed in the high strain. They, as did other investigators, found that the hybrids developed leukemia at a later age than did mice of the inbred stock.

Hogreffe[35] in a recent report interpreted his data to imply that the inherited susceptibility for leukemia was dependent on a single dominant gene. This theory was based upon calculated incidences for the hybrid generations and not on the observed data. Regarding the calculated incidences the author stated: "But the statistical evaluation of these curves is so complicated that it is doubtful whether too much weight can be laid upon the calculated curves."

The possible effects of nursing upon the genesis of spontaneous leukemia in mice has been investigated in several studies. No significant effect was found by MacDowell and Richter,[61] Kirschbaum and Strong[47] and Kirschbaum.[44] A lowered incidence was seen by Barnes and Cole[7] in mice of the Ak stock when they had been nursed by females of a low leukemic stock but the fostered mice did not survive as long as did the controls and no increase in the incidence was noted in fostered mice of the low leukemic stocks. Furth, Cole and Boon[33] reported a lower incidence in mice of the Ak stock following foster nursing but the incidence among the progeny of the fostered Ak animals was the same as in the control or unfostered group.

To test the theory that genetic ratios could be obtained only by classification according to progeny test, MacDowell, Potter and Taylor[62] mated females from an inbred low leukemia strain "(a) with a single male from an inbred high leukemia strain, (b) with 7 of the F_1 sons, and (c) with 50 of the backcross grandsons. Each of the 50 backcross males was described in terms of the incidence of spontaneous leukemia among approximately 50 of its second backcross offspring (total 2,677 diagnosed autopsies). With the aid of nurses from another supposedly low leukemia strain, all these mice were raised in the same season of the same year. The incidence of leukemia in these 50 families ranged from 0 to 42.8 per cent, with a mode at 17 to 20 per cent."

The conclusions from this study were:

"This variation between families far transcends the variation caused by certain extrinsic influences not equalized by the experimental procedure, and constitutes evidence that the fathers of the first backcross were genetically diverse, as the result of the segregation of genes influencing the incidence of leukemia.

"The study of other variables revealed a complex interrelationship of influences modifying the length of life, with differing effects upon the incidence of leukemia, as

indicated in the following suggested interpretation. One influence, which varied according to the backcross father, lengthened the lives of leukemics and negatives without changing the incidence of leukemia. Nurses of one strain lengthened the lives of male negatives and raised the incidence of leukemia among males. This same nurse influence, acting on leukemics, lengthened the lives of both males and females, especially those that early manifested the disease, without thereby changing the incidence of leukemia. Femaleness lengthened life by resisting certain nonleukemic causes of death, thereby increasing for females the opportunity for potential leukemics to appear. But the sex difference in incidence was less consistent than the sex difference in length of life of negatives, because femaleness, to a smaller extent, also resisted leukemia. The increasing parturition age of the mother progressively delayed the appearance of leukemia, without influencing other causes of death, with the result that more and more of the potential leukemics died from other causes and the incidence of leukemia fell as the mother's age increased. Youngest mothers revealed most accurately the potential leukemics, and the evidence of genetic differences between the second backcross families depends on young mothers; for the oldest mothers virtually eliminated leukemia, whatever the genetic tendencies of the family."

Recent reviews on leukemia in mice have been published by Furth,[32] Engelbreth-Holm[29] and Kirschbaum.[45]

GENETICS OF SPONTANEOUS LUNG CANCER

Few workers have attempted to study the transmission of susceptibility for spontaneous pulmonary tumors, probably because the time element for the average cancer ages, in inbred strains and hybrid mice, may range from nineteen to twenty-eight months. However, many experiments have been completed upon the induction of these tumors by hydrocarbons in which results may be obtained within a period of a few months. References for the work on induced lung tumors may be found in a recent article by Little.[53]

Using the best strain available at the time Lynch, in a series of publications,[57–60] showed the tendency to develop lung cancer to be transmitted as a dominant complex. Environmental factors were also of some significance. When mice of the A strain, in which the incidence of lung tumors in virgin females was found to be 89 per cent, were mated with animals of the low cancerous B stock, the data obtained in the reciprocal hybrids, based upon the incidences and average cancer ages were interpreted in accord with the genetic theory that the susceptibility was transmitted as a single dominant factor.[11,27] This simple explanation was probably in error, as has been pointed out by Heston.[36]

A few figures from this experiment may be of interest. Whereas some types of cancer are either palpable or may be noticed a short time after development, a positive diagnosis of lung cancer is possible only following an autopsy to be confirmed by microscopic examination of the section. In the experimental series of the A strain the youngest female to be observed with lung cancer was 303 days, the oldest 791 days, with an average cancer age of 585 days or 19.5 months. In another group of mice of the same stock killed at 271 days, seven of twenty mice were found to have lung nodules although none of the mice showed symptoms of the disease. Thus, the animals may have tumors for some months before they show any physical signs. In the reciprocal F_1 hybrids the youngest mouse which was killed because of its physical condition and found to be cancerous was 563 days while the oldest survived for 1,102 days. The average cancer age in the F_1 female population was 26.7 months, 7.2 months later than was observed for females of the inbred A stock. The difficulties encountered in keeping the animals alive for such a period are obvious.

Heston[36] used mice of the same A strain and animals of the L stock as the low cancerous line and the incidences were determined by killing the mice at specific periods, viz: twelve, fifteen and eighteen months. At the later age the incidences in the A, L, F_1 and L backcross animals were 90 per cent, 0 per cent, 53 per cent and 22 per cent, respectively. These results, where the F_1 results were intermediate at different ages between the two inbred parental strains, suggested multiple-factor inheritance. Heston also thought environmental factors to be of some importance. The average cancer ages for the respective groups were not determined but had the average age in the F_1 hybrids been seven months later than was found in the inbred cancerous strain, as reported above, hybrids living to that age should have been observed instead of eighteen months, a period which would correspond closely with the average cancer age for the A strain.

Approximately 90 per cent of the breeding females of the A strain with the mammary tumor milk agent will develop mammary cancer and consequently only a few will survive to the age at which lung tumors would be expected. However, it is possible to reduce the incidence of mammary tumors as the result of foster nursing.[10] When such a group of breeders was observed it was found that they showed a lower incidence of lung tumors than did non-breeders of the same strain at comparable age periods. The incidence in the breeding group was 51 per cent, average age 18.3 months, whereas the virgins showed an incidence of 89 per cent at 19.5 months. In the breeders without the milk agent the incidences of lung tumors were approximately the same in mice of the fostered generation, the progeny of fostered mothers that died with lung cancer and the progeny of fostered mothers were non-cancerous when they were autopsied.[14] The significance of these data is not apparent but suggests that increased hormonal stimuli may possibly either delay or inhibit the development of lung cancer.

GENETICS OF SPONTANEOUS MAMMARY CANCER

Research on the etiology of mammary cancer in mice dates back for at least forty years and has been reviewed in several publications.[18,22,23,24,36,54,55,69,71] Since the early workers either used strains that were not adequately inbred or animals obtained from commercial dealers, it was to be expected that they did not obtain analogous results and no common theory could be acceptable to all. That this type of neoplasm was found in certain lines was soon noticed. The role of the hormones in the development of mammary cancer was demonstrated by the work of Loeb, Murray, Cori and others, and these results were later confirmed by the use of synthetic hormones.

The modern trend for investigations in this field was initiated by the studies of the Staff of the Jackson Memorial Laboratory[43] and Korteweg.[48] In these experiments reciprocal crosses were made between inbred strains of mice with either high or low incidences of spontaneous mammary tumors and the hybrids were continued as either virgins or breeders. In every cross the offspring descended from mothers with low incidences had low incidences whereas those from maternal parents with high incidences gave high incidences. Thus, some maternal influence was demonstrated in the genesis of mammary cancer in mice.

Various explanations were advanced to account for this maternal or extrachromosomal influence. Cytoplasmic transmission[49,50,51,66] was assumed to be the probable route and later an intrauterine,[30] without any other maternal influence, was thought to be of importance although previously published data[2,10,12,13,27,64,75, etc.] had shown the latter to be of little if any significance.

Several thousand mice of the various hybrid generations were observed by Murray and Little[65–68] in the cross between the cancerous dilute brown and low cancerous C_{57} black stocks. Conclusions from their 1939 paper[68] were: "Some extrachromo-

somal influence, which is ten times as powerful as any possible chromosomal factor, is instrumental in determining whether or not mammary cancer appears in the first out cross generation" and "The tendency to have mammary cancer is not mendelian in nature."* From their 1936 publication[66] it is possible to secure an explanation of what is implied by extrachromosomal influence from the following: "Mammary tumors of epithelial origin are transmitted largely by means of extrachromosomal influences" and "From this it is apparent that in these crosses which derive their cytoplasm from non-tumorous mothers (A and C) the incidence of breast tumors is significantly less than in those crosses which get their extrachromosomal influence from the mother of the cancerous stocks. . . . "

The foster nursing study was started in 1934 and the results were reported two years later.[10] The young mice born to mothers of a high cancerous strain were removed soon after birth and were transferred to and raised by lactating females of a strain with a low incidence of mammary cancer. The fostered mice and their descendants showed few mammary tumors, demonstrating that the maternal or extrachromosomal influence was transferred in the milk. This milk-borne influence is generally referred to as the mammary tumor milk agent or milk agent. A few of the fostered mice developed mammary tumors as did their progeny; other fostered mice died noncancerous and yet their progeny showed a rather high incidence. These observations indicated that some of the young received the milk agent from their mothers before they were transferred.† Taking the progeny by cesarean section[3] or searing the nipples of the mother[4] is more certain to eliminate the milk agent than waiting until the young have been born and have had the opportunity of nursing.

Without presenting the details of numerous experiments by many investigators, it may be stated that the mammary tumor milk agent has the properties of an infectious agent or virus. The early studies of several workers demonstrated the role of hormonal stimuli in the genesis of the disease and the basis for genetic factors will be discussed in this report. In 1939 a theory[12,13] was advanced that the development of mammary cancer in mice generally depended upon the action of three factors: (1) the mammary tumor milk agent, (2) hormonal stimulation and (3) inherited susceptibility. In these reports it was shown that a low incidence would be observed if any one of the primary causative factors was not present or active, or as stated recently by Heston:[37] "Mammary tumors do not result from any one of these factors or sets of factors, but from the actions and interaction of all three, and it would be folly to attempt to say which is the more important."

After the mammary tumor milk agent had been demonstrated various strains with low incidences were tested by fostering the young mice on females with high incidences in an attempt to find a strain that would remain free from mammary tumors, one that might be called "non-susceptible." Andervont[5] has reported that mice of one line of the C_{57} black or B stock have remained non-cancerous but to date they have not been used extensively for genetic studies; other lines of this strain have given

* This would refute a statement in a recent review[55] that chromosomal influences were first suggested in these reports. Two publications[12,13] published previous to one of these papers,[68] in which genetic susceptibility was shown to be a primary factor in the genesis of mammary cancer, will be considered later in the summary of the literature. To the suggestion that the genetic constitution of the host might be a primary contributing cause of mammary cancer in mice, Little[52] wrote in 1941: "The exact degree of this influence is, however, undetermined, and it is certain that it plays a minor role in determining the incidence of this type of tumor."

† Animals descended from a female of the first litter to be fostered in 1934 are being continued and the line is now over thirty-five generations removed from the parental cancerous A strain in which fifty-seven successive generations of mammary cancer have been recorded. In the fostered A stock, called Ax, one mammary tumor has been recorded among several hundred breeders during the past seven years. A litter of the thirty-second generation of the Ax line was permitted to nurse a female of the cancerous A strain with the milk agent—tumors are being observed in these mice and their progeny. Comparable data may be obtained by the injection of extracts with the agent.

incidences in excess of 10 per cent and one was found to be high cancerous and remained so for at least twelve generations.[6] Such observations make it difficult to state the exact genic make-up of the inherited susceptibility for mammary cancer; because if one assumes that a line with an incidence of 10 per cent is "non-susceptible" when they have the milk agent and the hormonal stimulation resulting from the production of young and lactation, one must consider the possibility that either some tumors may arise in these animals from the action of the agent and the hormones or the mice are not homozygous. No strain should be said to be non-susceptible until breeding mice with the milk agent have been observed.

The reciprocal cross between the cancerous A and low cancerous B or C_{57} black stocks was the first study, with adequate controls, to indicate the role of the genetic susceptibility as a primary factor in the genesis of mammary cancer in mice after the mammary tumor milk agent had been identified. That the hormonal stimulation associated with pregnancy and lactation was required for the development of mammary cancer in females of the A strain was obvious since the virgins have a low incidence and the breeders an incidence in excess of 90 per cent. Few mammary tumors are to be found in breeders of the B stock which do not possess the milk agent; two groups of mice with the milk agent, used as controls, were found to have incidences of 11 per cent[15] and 18 per cent.[20]

The F_1 hybrids descended from females of the A strain with the milk agent showed incidences corresponding with those found in the maternal strain—low in virgins and high in breeders. Hybrids with mothers from the strains with low incidences, C_{57} black and fostered A, showed few tumors. Reciprocal foster nursing was done and it was determined that among breeding females the hybrids with mothers from the low cancerous strain but nursed by females of the high cancerous stock showed comparable data to the hybrids that had and were nursed by mothers of the high stock. While only the females of the reciprocal F_1 generations were fostered, there was no significant difference between the incidences of the F_2 and F_2 descendants. In the various hybrid generations evidence for the segregation of the genes that controlled the inherited susceptibility for mammary cancer was indicated.[12,13,17,21]

The conclusions from this study follow:[21]

"Reciprocal F_1 hybrids produced by mating mice of one low cancer (C_{57} black) and one high cancer (A) strain and nursed by females of the cancerous stock gave, in breeding females, approximately the same incidence of spontaneous mammary cancer.

No evidence was secured to suggest any intrauterine influence for the development of mammary cancer in mice.

The incidence in the total number of F_1 hybrids nursed by females of the A stock did not differ significantly from the incidence secured in mice of the cancerous A stock.

Although the pooled data obtained in all the hybrid generations could be accounted for on the genetic theory that the inherited susceptibility for mammary cancer in this cross was transmitted as a single dominant factor, it becomes evident on analysis of the incidence of cancer in the several subgroups that such a simple interpretation is inadequate and that other factors are probably involved. Detailed analysis shows: (1) that the incidence of mammary carcinoma in the F_2 hybrids with brown coat color was significantly higher than in their litter mates with black or albino coats; (2) that not all brown mice become cancerous, nor was the incidence in brown mice as high as in mice of the high cancerous A stock; (3) the progeny of brown mothers had a higher incidence than did the progeny of black or albino mothers, but not all brown mothers transmitted the inherited susceptibility to their progeny; (4) the incidence of cancer was significantly greater, in some groups, in the mice born in the third and later litters than in mice born in the earlier litters from the same mothers; (5) the incidence in the progeny was in-

fluenced also by the age at which the mothers developed mammary cancer.

It has previously been shown that a considerable proportion of mice of the so-called non-susceptible stock developed mammary cancer when given the active milk agent. Therefore, even mice of these strains are not totally resistant, and either they must possess certain factors conducive to mammary carcinoma production or the tumors must result from extrinsic and/or metabolic inciting influences. Obviously the mice of low cancer strains do not have all the inciting factors that are present in mice of the high cancer strains.

If some mice of a genetically non-susceptible strain develop mammary cancer, it is probable that some cancerous hybrid animals are likewise non-susceptible. Thus the incidence would not represent the true percentage of susceptible animals, and should not serve as the only basis for a genetic interpretation of the data.

It is concluded that the inherited susceptibility for spontaneous mammary cancer in mice, as transmitted by mice of the cancerous A stock, probably depends upon multiple genetic factors, one of which may be linked with the gene for brown coat color.

After the maternal influence for mammary cancer[42] had been demonstrated but before it was found to be transferred in the milk,[10] it was noted that when two high cancerous strains, with different incidences and average cancer ages, were crossed, the incidences and ages seen in the reciprocal hybrids might be correlated with those found in the maternal strains.[9] In such a cross the F_1 hybrids would be expected to have the same genetic constitution and so any variation in the cancer data might be explained as resulting from the action of perhaps different agents from the cancerous strains. Also, when males of different strains were mated to females of the same cancerous stock, Andervont[1] found considerable variation in the resulting F_1 hybrids.

Van Gulik and Korteweg,[75] Murray and Little[65–68] and Murray[64] used the same strains in their investigations but obtained considerable variation in their results. The former workers found that the hybrids with mothers from the cancerous stock gave an incidence of 69 per cent while the reciprocal hybrids nursed by females of the cancerous stock showed 46 per cent. In 1935 Murray and Little[67] observed in the dilute brown x C_{57} black cross that the hybrids with mothers of the cancerous strain had an incidence of 40 per cent; in 1941[64] the hybrids with mothers from the low cancerous strain but nursed by females of the dilute brown stock showed an incidence of 65 per cent. During the interval the incidence in the virgins of the cancerous strain had increased from 51 to 62 per cent; thus these data, collected in different laboratories, may not be considered as control observations.

When females of the cancerous lines of the A and C_3H stocks were mated with males of the respective lines of fostered mice of these strains without the milk agent, approximately the same incidences were secured in the F_1 and F_2 generations as in the maternal strains.[16,19]

Many other observations from analogous experiments might be cited but they have been summarized in a recent review.[24]

GENETIC CONTROL OF HORMONAL MECHANISMS

Mice of the inbred A strain are genetically susceptible for the development of spontaneous mammary carcinoma and a high incidence will be obtained in females when they are maintained as breeders but not more than 5 per cent of the virgin females will give rise to such tumors. In contrast to these data, both the virgin and breeders of the C_3H stock have high incidences. Two independent reports[26,38] were published in 1944 which explained the difference in the incidences between the virgins of the A and C_3H stocks as resulting from the genetic control of the hormonal mechanism. The factor has been termed the inherital hormonal influence[22] and is associated with the development of mammary cancer in non-breeding females. Further studies showed that the same genes proba-

bly do not determine the inherited susceptibility for mammary cancer and the inherited hormonal influence[25] although common genes may exist.

By grafting ovaries from A, C_3H and F_1 animals into spayed F_1 females in which the grafts would be subjected to comparable pituitary stimulation and the hormones produced would be metabolized and act upon the same tissues and end organs, it was determined that part of the physiologic effects of the inherited hormonal influence was due to an inherent ovarian function.[40–42]

When day-old mice were ovariectomized, Woolley and his associates[76–78] observed that those of certain strains showed hormonal stimulation of the secondary sex organs and a few of the castrated animals developed spontaneous mammary tumors. They found the source of the hormonal stimulation to be the adrenal cortex which had become hyperplastic and/or tumorous.

In mice of the A and C_3H stocks and their hybrids, a correlation has been noticed between the inherited hormonal influence and hyperplasia of the adrenals in castrated animals.[72–74] That is, females of the C_3H stock and the hybrids—groups that may show high incidences of mammary tumors when kept as non-breeders—showed the adrenal changes following the removal of the gonads. Many of the castrated females developed mammary cancer. No evidence for hormonal stimulation was to be found in the ovariectomized females of the A strain and the secondary sex organs remained in the castrate state. In this study the mice were approximately four weeks of age at the time of operation.

These observations have been extended by determining the castration effects in several other stocks by Huseby and the author.[44–41 and unpublished] Males of strains that showed any adrenal changes were mated with females of the A strain that have a low incidence of mammary tumors in virgins. In the castrate F_1 hybrids of these crosses, the histologic changes to be found in the adrenals were usually analogous to those seen in mice of the paternal stocks. The high incidences of mammary tumors in the virgin hybrid populations would indicate that the association between adrenal hyperplasia following castration and the inherited hormonal influence may be extended to include, in addition to the C_3H or Z stock, the C, I, and two sublines of the dilute brown strains.

The observations of Andervont[2] that mice of the I strain with the milk agent would show a low incidence of mammary tumors as breeders has been confirmed. Thus it appears that although they are relatively resistant for the development of mammary cancer, they transmit the inherited hormonal influence and the AIF_1 virgins have a high incidence.

Following castration, mice of the Ce strain were observed to develop adrenal carcinoma[79–85] and these tumors produced hormones with androgenic and/or estrogenic activity. When females of the Ce stock obtain the mammary tumor milk agent by foster nursing, the results demonstrate that they are susceptible for mammary cancer since 76 per cent of the ninety-five females continued as breeders have developed tumors; a low incidence has been seen in non-breeders.[24 and unpublished]

The incidences of mammary tumors were determined in hybrids produced by mating A females with Ce males. Castrate F_1 hybrids developed adrenal cortical tumors.[44–41] While the incidence of mammary tumors noted in $ACeF_1$ virgins was higher (37 per cent) than was seen in the virgin females of the A strain (4 per cent),[25] it was significantly lower than was observed in the previously reported crosses (over 70 per cent) between A females and males of strains that showed primarily adrenal hyperplasia following ovariectomy.

The incidences of mammary tumors observed in the reciprocal F_2 breeding females of the A x C_3H cross were approximately the same as found in the maternal stocks. However, the breeding F_2 females of the A x Ce cross showed an incidence of 58 per cent, considerably lower than was found in either parental stock. When females of the Ce stock with the milk agent were mated to

C_3H males, the F_1 virgins have had an incidence of 80 percent while in the breeders over 90 per cent have had mammary tumors. Preliminary data may be cited for the $ZCeF_1$ cross (Z or C_3H females x Ce males). In a group of virgin F_1 females fifty-nine of the sixty-one mice which have died have had mammary tumors, in depleted litters the incidence has been 93 per cent at an average age of 366 days.

Non-castrated females of the Kirschbaum line of the Strong NH stock will show adrenal adenomas and the time of appearance of these tumors may be accelerated by castration.[31,46] Following gonadectomy, females of the JK stock, obtained from Strong, will develop adrenal hyperplasia (Huseby and Bittner, unpublished). It has also been determined that when males of these two strains are mated with females of the A strain, the castration effects in the $ANHF_1$ and $AJKF_1$ hybrids are analogous to those seen in the respective paternal stock. If these hormonal effects might be associated with the inherited hormonal influence, one would expect that $AJKF_1$ and $ANHF_1$ virgins would have high incidences of mammary cancer but instead they show low incidences. A small number of breeders of each group is being observed and they likewise are not having the high incidences that have been characteristic of hybrids descended from females of the A strains.

Males of the JK and NH stocks have also been mated with females of the Z or C_3H strain. The $ZNHF_1$ virgins are having a high incidence and more than 90 per cent of the mice which have died have had tumors (in depleted litters, 94 per cent). None of the $ZJKF_1$ virgins are more than ten months of age but several spontaneous mammary tumors have been observed.

A low incidence of mammary tumors is being observed in JK breeders with the mammary tumor milk agent. However, mice of the fostered generation and their progeny will transfer the milk agent as determined by observing JK x Z hybrids. Mice of the NH stock have not been tested. The data from these various crosses would indicate that the various strains may possess different hormonal mechanisms and the physiologic effects of these are transmitted, as determined by gonadectomy in hybrid animals. Furthermore, these hormonal mechanisms do not show the same influence upon the genesis of mammary cancer in the hybrids when they are maintained as non-breeders.

SUMMARY

Many inbred strains of mice have been selected which differ in their inherent ability to develop various types of spontaneous neoplasms. This material is to the biologist what pure chemicals are to the chemist. However, as animals are subject to mutational changes, each experimental series should have adequate controls. Many studies have been reported on the influence of environmental factors upon the genesis of cancer and consequently data obtained in one laboratory should never be used as controls for those secured elsewhere. Only the experimental variable being tested should exist between the animals of the two groups.

Reciprocal crosses between inbred strains with either high or low incidences of tumors have demonstrated that the genetic constitution of the host plays an important part in the genesis of leukemia, pulmonary and mammary cancer in mice. In the case of leukemia, while most of the workers agree that susceptibility may be transmited as a dominant complex, the number of genes could not be ascertained because of the action of undetermined environmental factors or, according to MacDowell,[62] a complex interrelationship of modifying influences. Certain unknown factors probably operate also in the development of lung carcinoma and the development of the disease in very old animals makes it difficult to obtain ratios for genetic interpretation.

Three primary factors have been demonstrated to interact in the development of spontaneous mammary tumors—genetic susceptibility, hormonal stimuli and a virus, the mammary tumor milk agent. In several

studies low incidences have been found in mice that possessed the milk agent and had an adequate hormonal stimulation. Such groups may be considered to be relatively resistant; whether they may be called "non-susceptible" or not is problematic.

The interaction of these primary causative factors is complex as shown by the observations that reciprocal hybrids between various cancerous strains may or may not have the same incidences and average cancer ages. The difference observed between two groups of susceptible mice with different agents may be of statistical significance whereas reciprocal groups with the same genetic constitution and milk agent may or may not show comparable data. If two groups of virgin females show a significant variation in incidence and average cancer age, there may be no difference in the incidences in the breeders and the group with the later age as virgins may have an earlier cancer age when maintained as breeders (unpublished).

Although not characteristic for all series, in one study the incidence found among the progeny was influenced by the age at which the mothers developed cancer and the litter in which the young were born. Also, the young fostered by mothers that die either cancerous or non-cancerous may show different incidences, regardless of the genetic constitution of the mothers.[39] Analogous results may be noted for the progeny of females of the same litter of an inbred stock.

The genetic constitution of the animals also plays an important role in controlling various hormonal mechanisms, one of which, called the inherited hormonal influence, may influence the development of mammary cancer in virgin mice. Various studies were cited to determine the physiologic effects of these hormonal factors and their possible relationship to the genesis of mammary cancer in inbred stocks and their hybrids.

Recently it was observed that mice of inbred strains and their hybrids with the mammary tumor milk agent excreted less 17-ketosteroids than did mice of the same stock, or hybrid generation, without the agent.[70] The injection of extracts with the agent[24] altered the excretion rate to that found for animals which obtained the milk virus by nursing. Considerable difference was noted between various susceptible strains. In most of the groups, but not all, the presence of the milk agent was associated with an increased number of positive smears observed during a definite period.[40]

The long interval between the introduction of the mammary tumor milk agent, a virus, and the appearance of spontaneous mammary cancer would become apparent if the virus had some role in controlling the metabolism of the hormones. Through such a process the mice with the milk agent might possess an excess of what might be called "carcinogenic" hormones as compared with mice without the agent. These hormones, acting upon susceptible cells, could be the "primary" cause of mammary cancer in mice although the interaction of all the causative factors would be required before a high incidence would be obtained.

Thus genetic factors have been demonstrated in the etiology of several types of tumors in mice. The exact genic make-up of the susceptibilities has not been definitely determined because of the possible interaction of other genetic and perhaps unknown "environmental" influences. In the cancerous A strain, linkage between one of the susceptibility genes for spontaneous mammary cancer and the brown gene has been demonstrated.

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Clinico-pathologic Conference

Respiratory Infection, Arthralgia and Renal Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, H. R., (No. 166935), a white married miner, forty-seven years of age, entered the Barnes Hospital on December 25, 1948, because of fever of unknown origin. The patient's mother died of heart disease and one sister had had cancer but otherwise the family history was non-contributory. Except for typhoid fever and smallpox in early life his general health had been good. He felt entirely well until five weeks before entry when he developed a mild upper respiratory tract infection with which there was associated slight cough and malaise but no sore throat. Two weeks later pain in the joints of the hands, wrists, shoulders, feet and ankles suddenly appeared. There was swelling of the phalangeal joints but of no others. The patient consulted a physician and was told that he had arthritis; he was given two injections of penicillin, each 300,000 units, followed by ten injections of streptomycin in a dosage not known. The joint pains persisted for several days and were so severe that the patient was unable to walk. After a few days although the signs of arthritis gradually subsided, the patient's temperature which at the outset had been 101°F., persisted as did the general malaise with which he was afflicted.

Eight days before entry the patient noted tenderness in the left calf. He was again seen by his physician who gave him an injection of a respiratory penicillin preparation, advised him to remain in bed and bandaged his leg tightly. The next day the patient had dull pain along the left costal margin which was made worse by deep respiration. Although the pleuritic pain persisted, tenderness in the left calf disappeared. One week before entry to the Barnes Hospital the patient was taken to the hospital in the community in which he lived. There it was said that his red blood count was low and he was given liver and vitamin injections. While in that hospital blood cultures, agglutination tests for typhoid, paratyphoid, brucella and typhus were all said to have been negative and a chest film was read as normal. He was transferred to the Barnes Hospital for further study.

At the time of entry his temperature was 38°C., pulse 80, respirations 20 and blood pressure 134/78. The patient was a well developed, rather pale man who appeared moderately ill and rather weak. Slight pain on motion of several of his joints was noted but no signs of acute inflammation were observed. There were two small petechiae in the left conjunctiva. The pupils reacted to light and accommodation and the eyegrounds were entirely normal. Examination of the upper respiratory tract was negative. The thyroid gland was enlarged to one and one-half times its normal size and there was a very small nodule in the lower pole. The neck veins were not distended and the lungs were clear to percussion and auscultation. The heart was not enlarged. A grade 2, rather harsh systolic murmur was heard at the apex but it was not transmitted. The rhythm was regular; the sounds were of

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good quality. The splenic tip was felt 5 cm. below the costal margin and was described as soft and tender. A loud friction rub could be heard over the spleen and over the left lateral chest wall. The liver edge was palpated just below the costal margin on the right and also was described as soft but it was non-tender. There was no costovertebral angle tenderness. Rectal examination revealed only slight induration of the right lobe of the prostate. On examination of the extremities there was minimal tenderness over the left calf and a questionably positive Homans' sign on the same side. A slight coarse tremor of the extended fingers was apparent but clubbing was only questionable. The neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 3,900,000; hemoglobin, 11 gm.; white cells, 14,250; differential count: eosinophiles, 1 per cent; juvenile forms, 1 per cent; segmented forms, 79 per cent; lymphocytes, 13 per cent; monocytes, 6 per cent. Urinalysis: specific gravity, 1.010; albumin, negative; sugar, negative; centrifuged sediment, fifty to sixty red blood cells per high power field. Blood chemistry: non-protein nitrogen, 45 mg. per cent; total protein, 6.7 gm. per cent; albumin, 3.7 gm. per cent; globulin, 3.0 gm. per cent. Stool examination: guaiac positive. Blood Kahn test: negative. Blood culture (on admission): no growth. Sputum culture: heavy growth of coliform organisms. Agglutinations versus brucella, tularence and typhoid antigens: negative. Electrocardiogram, P-R interval: 0.21 seconds; no other abnormality. Roentgenogram of the chest: "A chest film reveals the cardiac shadow minimally enlarged to the left; there is slight lengthening of the aorta; a minimal degree of peribronchial infiltration is seen in the posterior portion of the right lower lobe and there is considerable pleural thickening in both apices."

After admission repeated urinalyses showed the specific gravity to range from 1.008 to 1.012; 1 to 2+ albuminuria was also noted as were many red blood cells in the centrifuged sediments. A blood culture drawn on the third hospital day was positive for alpha hemolytic streptococcus; the organism was reported sensitive to 0.2 units per cc. of penicillin but not to 0.05 units. Following the positive blood culture report the patient was placed on a regimen which included 100,000 units of aqueous penicillin every three hours. During the course of the first week following the institution of penicillin therapy the patient's temperature, which had never exceeded 38.9°C., gradually fell to an average of 37.5°C.; on the twelfth hospital day it became normal. Although the patient appeared comfortable and without complaint, the non-protein nitrogen during this period rose to 135 mg. per cent. Six blood cultures taken at intervals following the institution of penicillin therapy were sterile. On the thirteenth day the patient suddenly complained of left upper quadrant pain and his temperature rose to 39°C. Examination revealed marked tenderness over the splenic area. Re-examination of the eyegrounds showed that they were still normal. Two weeks after admission the following blood chemistry studies were reported: non-protein nitrogen, 105 mg. per cent; total protein, 7.4 gm. per cent; albumin, 4.0 gm. per cent; globulin, 3.4 gm. per cent; carbon dioxide combining power, 24.6 mEq./L.; chlorides, 98 mEq./L.; calcium, 9.2 mg. per cent; phosphorus, 11.7 mg. per cent; alkaline phosphatase, 2 Bodansky units. Red blood count, 3,230,000; hemoglobin, 7 gm.; white blood cell count, 11,100 with 9 stab forms and 57 segmented forms.

Because of the anemia the patient was given several blood transfusions. In the ensuing period his temperature again returned to approximately normal values and remained there. Repeated determinations of the non-protein nitrogen showed it as high as 168 mg. per cent. The blood phosphorus remained at about 11 mg. per cent. Following another blood transfusion the patient felt better, and during the following week there was no change of note either in his clinical condition or in the various blood

chemical studies. He was placed on an alkaline ash diet containing 50 gm. of protein daily and was given amphojel in order to decrease the absorption of phosphorus from the gastrointestinal tract. The nonprotein nitrogen fell to 125 mg. per cent but hematuria and albuminuria persisted and the patient began to have rather severe vomiting. The serum chlorides fell to 82 mEq./L. and his clinical condition deteriorated as evidenced, among other things, by diminution in urinary output. The patient was unable to retain any food by mouth and was given parenteral infusions of glucose in saline.

Three days before death he coughed up dark red and partially clotted blood. At this time his temperature was 37.3°C. and there was some puffiness noted about the eyes. The fundi continued to appear normal. The neck veins were slightly distended. Respirations were rather shallow and moist rales were heard at both bases. Examination of the heart was unchanged from that on admission; abdominal examination was likewise unchanged. There was slight pitting edema of the lower extremities. Questionable tenderness of the left calf was again noted. The Homans' sign was now definitely negative. Repeat x-ray films of the chest revealed infiltration of the left upper and right middle and right lower lung fields. There was a small amount of fluid in the left costovertebral angle. The venous pressure was found to be 130 mm. of water and the circulation time with decholin 13 seconds. In addition to mild dyspnea the patient complained of pain in the anterior chest, and a definite pericardial friction rub was heard. The red cell count had fallen to 1,720,000, the hemoglobin to 4.6 gm. and the white cell count was 20,200. Determination of the blood sodium revealed it to be 125 mEq./L. with a potassium of 4.72 mEq./L. The carbon dioxide combining power had fallen to 16.3 mEq./L.; the chlorides had returned to a value of 97 mEq./L. Blood calcium was 7.9 mg. per cent and phosphorus, 10.9 mg. per cent. The icterus index was 9 units. Another electrocardiogram was normal. The patient continued to do poorly. The rales in his lungs increased and another chest film a day later revealed a definite increase in the pulmonary infiltration, particularly in the mid-portion of both lung fields. Following digitalization with lanatoside C. there was a rather dramatic improvement but it was only temporary. The patient's urinary output continued to fall. Hemoptysis persisted and two days before death his temperature rose to 39°C. Terminally there was an increase in the number of rales heard over the lung bases and on February 3, 1949, the patient expired quietly. During his entire hospital stay his blood pressure was never elevated and at no time did the character of his heart murmur change.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This is indeed an interesting situation wherein a man forty-seven years of age with no recorded significant illness in the past developed a respiratory tract infection with cough, fever and malaise but without a sore throat. Subsequently he became acutely ill with the manifestations enumerated in the protocol and he died within several months of the onset of this illness. It is of great interest that two weeks after the onset of the upper respiratory tract infection, although there was no apparent pharyngitis, the patient developed polyarthritis. The joints of his hands were particularly involved but he had enough pain in his other joints to prevent him from walking. Dr. Glaser, in your opinion, did this man have acute rheumatic fever?

DR. ROBERT J. GLASER: The diagnosis of acute rheumatic fever certainly must be considered seriously in this patient. The history presents the classic sequence of events seen in rheumatic fever, namely, an upper respiratory infection of rather mild nature followed two weeks later by the sudden onset of joint pain. Although as you have pointed out the patient did not complain of a sore throat, it is entirely conceivable that group A beta hemolytic

streptococci were present in his throat, and I believe acute rheumatic fever must be placed high on the list of possibilities.

DR. ALEXANDER: The only organism recovered in the one positive blood culture was an alpha hemolytic streptococcus. Is there any relationship between the alpha hemolytic streptococcus and acute rheumatic fever?

DR. GLASER: It is now almost the unanimous opinion of those interested in rheumatic fever that only group A beta hemolytic streptococci are of importance in the development of acute rheumatic fever. Some years ago studies with the alpha hemolytic streptococcus were pursued in an attempt to determine their role, but there is no good experimental or clinical evidence to incriminate this organism. Group A beta hemolytic streptococci, on the other hand, can be isolated in a very high percentage (from 70 to 90 per cent in a given series) of patients during the acute respiratory infection which precedes the attack of rheumatic fever. Much evidence in support of this point was gathered during the recent war in both army and navy installations. The alpha hemolytic streptococcus, which is also called Streptococcus viridans, is the infecting organism in many cases of subacute bacterial endocarditis.

DR. ALEXANDER: Several throat cultures were taken, none of which showed beta hemolytic streptococci. If one accepts the diagnosis of acute rheumatic fever, must he not postulate that the patient had beta hemolytic streptococci in his throat at some time?

DR. GLASER: Positive throat cultures are important but the failure to find beta hemolytic streptococci in cultures does not rule out the possibility of acute rheumatic fever, nor does it rule out the possibility that the patient was harboring beta hemolytic streptococci in his upper respiratory tract. Many of these patients have many more streptococci in their nasal passages than in their pharynx; and unless nasal cultures are taken, the organism may not be recovered.

DR. ALEXANDER: Cultures of the sputum showed only coliform organisms but the patient had received considerable chemotherapy on the outside and streptococci, even had they been present originally, may have been eradicated. At any rate it is fair to assume that the rather extensive antibiotic therapy which the patient received may explain our inability to recover the beta hemolytic streptococcus. Is it possible that this man may not have had acute rheumatic fever, Dr. Glaser?

DR. GLASER: It is entirely possible that he did not. For the sake of completeness one might mention the so-called poststreptococcal state, a syndrome characterized by arthritis and sometimes by minor electrocardiographic changes, which is considered by many workers in this field to represent mild rheumatic fever. If one wants to be less specific but more inclusive, he can say that the patient exhibited the poststreptococcal state.

DR. ALEXANDER: This attack was presumably his first and occurred at the age of forty-seven. Does the late onset trouble you?

DR. GLASER: It is often difficult to be sure that a given attack of rheumatic fever is the patient's first. Frequently in childhood mild, unrecognized attacks may occur of which the patient years later may have no recollection. Further, I remember Dr. Wood telling me once that he had seen what was thought to be an initial attack in a patient aged sixty-nine. Therefore, I do not think the fact that this man was forty-seven makes the diagnosis especially unlikely.

DR. CARL G. HARFORD: In view of the subsequent findings in this case I believe that the arthralgia perhaps could be explained on the basis of subacute bacterial endocarditis.

DR. ALEXANDER: That is a good point, Dr. Harford, for one certainly sees arthralgia in subacute bacterial endocarditis. What mechanism is involved in that situation, Dr. Harford?

DR. HARFORD: I am not sure that anyone knows. Perhaps emboli into the joint space may be responsible.

DR. THOMAS H. HUNTER: I do not think it is clear that the arthralgia in bacterial endocarditis is due to embolic phenomena but I know of no other adequate explanation for its occurrence.

DR. ALEXANDER: On occasion the arthralgia which is seen in proved subacute bacterial endocarditis is explained on the basis of an exacerbation of acute rheumatic fever.

DR. W. BARRY WOOD, JR.: I think that explanation is certainly tenable; it is supported by the studies of several investigators.

DR. HUNTER: Indeed there are those who believe that practically every patient who has subacute bacterial endocarditis has a concomitant attack of acute rheumatic fever.

DR. WOOD: Dr. Alexander, I should like to make one other suggestion. Although we have no history of it, this patient may well have received sulfonamides for the treatment of his respiratory tract infection—certainly many patients who acquire such infections do receive sulfonamides. The subsequent course, characterized by a clinical picture resembling that of glomerulonephritis without hypertension, brings up the possibility of sulfonamide hypersensitivity. I should like to suggest that diagnosis as a third possibility.

DR. ALEXANDER: Sulfonamide hypersensitivity should certainly be included in the differential diagnosis. In regard to subacute bacterial endocarditis it is of interest that five blood cultures taken on the first two days of hospitalization were negative; on the third hospital day, however, alpha hemolytic streptococci were recovered in one culture. In addition the patient had an enlarged, tender spleen, several conjunctival petechiae and a heart murmur. These signs and the laboratory findings certainly suggest strongly the possibility of subacute bacterial endocarditis. What explanation, Dr. Harford, can you offer for the fact that the first five blood cultures were negative? Do you believe that the therapy which the patient received before coming to the hospital may have been responsible for this sequence of results.

DR. HARFORD: I think it is entirely conceivable that the previous antibiotic therapy, although inadequate, may have controlled the bacteremia temporarily.

DR. ALEXANDER: Dr. Taussig, would you care to predict what lesions will be found in this man's heart?

DR. BARRETT L. TAUSSIG: I believe this patient had rheumatic valvulitis, probably of the mitral valve; and if he had bacterial endocarditis, it must have involved that valve.

DR. ALEXANDER: Dr. Smith, do you believe that this patient had rheumatic heart disease? The x-ray film did not reveal an abnormal contour and there was only minimal enlargement.

DR. JOHN R. SMITH: It is entirely conceivable that this man had mitral insufficiency without significant stenosis; if such were the case, the heart might well be almost normal in size and contour.

DR. ALEXANDER: Dr. Moore, you followed this patient. Were you particularly impressed by the murmur?

DR. CARL V. MOORE: As I recall it, the murmur was only of grade 2 or grade 3 intensity at the most and was rather well localized to the apex. On the numerous occasions I listened to it it did not change in quality.

DR. ERNEST T. ROUSE: I would like to confirm Dr. Moore's observations. The murmur persisted at the apex but was never transmitted elsewhere. Throughout the six weeks the patient was in the hospital I considered it of grade 2 intensity and never noted a change.

DR. ALEXANDER: Did not the heart become larger, however, during hospitalization?

DR. WOOD: A number of other factors such as the anemia, renal insufficiency and probably slight heart failure may have explained the subsequent enlargement of the heart, Dr. Alexander.

DR. HUNTER: Is it possible that this patient had an interventricular septal defect? The description of the murmur does suggest

mitral insufficiency but the patient had a preponderant number of findings in the lungs, a fact which seems to me out of proportion to the general situation. If the hemoptyses arose from pulmonary infarcts, not as a result of thrombophlebitis in the legs but rather from bacterial vegetations in the heart, the diagnosis of interventricular septal defect would certainly have to be considered.

DR. ALEXANDER: I think that your suggestion is a valid one; its answer will have to come from the pathologists. Let us now turn to the renal manifestations. The patient had many of the signs of nephritis, namely, hematuria, albuminuria, azotemia and a fixed specific gravity. Dr. Schroeder, what are your views concerning the nature of this man's renal lesion?

DR. HENRY A. SCHROEDER: I do not think that he had acute glomerulonephritis. Rather I would postulate that he had focal embolic nephritis associated with subacute bacterial endocarditis and that over a period of weeks large segments of the kidney were infarcted. It is conceivable, of course, that he had chronic glomerulonephritis.

DR. HUNTER: In my opinion the duration of the process is entirely too short for one to explain the renal findings purely on the basis of focal embolic nephritis. I think such a situation would be most extraordinary.

DR. ALEXANDER: I would agree with you, Dr. Hunter.

DR. SCHROEDER: The size of the infarcts would determine the speed with which the process could achieve the changes seen here.

DR. ALEXANDER: Did this patient have an acute exacerbation of chronic glomerulonephritis?

DR. SCHROEDER: The progressive rise in the non-protein nitrogen with albuminuria but without hypertension seems to me to make that possibility unlikely.

DR. WOOD: Dr. Alexander, Dr. Hunter has just written the section for both the Nelson's Loose-leaf "Medicine" and the new edition of Cecil's "Medicine" on subacute bacterial endocarditis, and I think it would be very proper to ask him how often patients with subacute bacterial endocarditis die of renal insufficiency arising as a result of the bacterial endocarditis *per se*.

DR. HUNTER: I cannot quote an exact figure, Dr. Wood, but I would say that at this stage of the disease, with an apparent duration of only six or eight weeks, it would be most extraordinary for a patient to die of renal insufficiency arising purely as a result of bacterial endocarditis. In neglected cases of bacterial endocarditis or in the occasional case in which all therapy is of no avail it is not unusual to see a patient die with renal insufficiency as the terminal event; but those patients usually have courses which last for months.

DR. WOOD: In this patient the determination of the antifibrinolysin titer might well have been helpful in determining whether the patient had either rheumatic fever or acute glomerulonephritis. I think that if the determination had been negative, the possibility of either one of those diseases would be definitely decreased.

DR. HUNTER: I think that an antistreptolysin titer would have been even more helpful.

DR. ALEXANDER: Dr. Flance, why did this patient cough up blood repeatedly?

DR. I. JEROME FLANCE: He certainly may have had multiple pulmonary infarctions, Dr. Alexander. He was also uremic and there is an increased tendency toward bleeding in uremia; therefore, one must consider the possibility that with pulmonary hypertension hemoptysis may be more prominent in uremia.

DR. HUNTER: Dr. Alexander, I am still concerned in regard to the nature of the renal lesion here. I believe that the pathologists will show us something other than either focal embolic nephritis or chronic glomerulonephritis. I would not be surprised if the patient had either a congenital anomaly such as polycystic kidneys or perhaps old, unsuspected pyelonephritis.

DR. ALEXANDER: In summary the concensus is that this patient probably had subacute bacterial endocarditis probably on the basis of old rheumatic mitral valvu-

lar disease. Whether or not he had acute rheumatic fever is much less clear. In regard to the renal lesion it has been suggested that the patient had subacute or chronic glomerulonephritis or focal embolic nephritis; finally, congenital anomaly, pyelonephritis and sulfonamide hypersensitivity have been postulated.

Clinical Diagnoses: Rheumatic heart disease, mitral insufficiency; subacute bacterial endocarditis due to alpha hemolytic streptococcus; ? acute rheumatic fever; ? nephritis, subacute, chronic or focal embolic; ? sulfonamide hypersensitivity.

PATHOLOGIC DISCUSSION

DR. THOMAS YOUNG: The right kidney weighed 270 gm. and the left 260 gm. The capsules stripped with slight difficulty to expose a smooth surface which was reddish yellow with numerous, widely scattered, discrete, punctate red spots. The cut surface bulged and the cortex was unusually thick. Petechiae were also present on the cut surface, predominantly in the cortical portion. On closer inspection tiny, grayish granules over the cut surface of the cortex were visible. The pelves were not dilated or thickened but beneath the mucosa there were confluent, irregular, purplish red foci of hemorrhage.

Together the lungs weighed 2,700 gm. Some tenuous adhesions bound each lung to the anterior and posterior chest walls. They were dark purplish red and the cut surface of all lobes oozed copious quantities of fluid of similar color. Although all lobes were the site of black, firm, anthracosilicotic nodules in moderate numbers, they were more numerous in the upper lobe of the left lung. There were fibrous scars in the apex of each lung; calcified nodules were present in the upper and lower lobes of the right lung and a right bronchopulmonary lymph node was seen. In the right pleural cavity there were 150 cc. of serosanguineous fluid that contained a small amount of fibrin; in the left there were 10 cc. of similar fluid.

The visceral and parietal surfaces of the pericardium were covered with patches and streaks of loosely adherent, friable, granular fibrin. Within the sac there were 30 cc. of yellowish green, cloudy fluid. The heart weighed 400 gm. The leaflets of the valves were supple, thin, translucent and free of verrucae or vegetations.

The liver was of normal appearance except for a hemangioma 1 cm. in diameter beneath the anterior superior surface of the right lobe. The spleen weighed 100 gm. and was adherent to the diaphragm. The cut surface was firm and without pathologic change except for grayish black streaking that roughly outlined the trabeculae.

There was altered blood in the upper gastrointestinal tract and a few petechiae and ecchymoses dotted the mucosal surfaces of the intestine and stomach. The thyroid was not enlarged but at the lower pole of the left lobe there was a crescent-shaped bit of yellow tissue 3 mm. in diameter.

The other gross anatomic findings were incidental and not of significance.

DR. ROBERT A. MOORE: Despite the features of this patient's history that were suggestive of disease in other organs, the significant anatomic changes involved principally the kidneys and a gross diagnosis of subacute glomerulonephritis was made. The reasons for that diagnosis are many. First, the kidneys were increased in weight. Second, the disease was one which involved the cortex to a greater extent than it did the entire kidney, for the cortex was 12 mm. in thickness and the medulla 16 mm. in contrast to the normal respective measurements of 8 and 16 mm. Third, when the surface of the cut section of the kidney was viewed tangentially, there were numerous, tiny, white, elevated nodules which were relatively bloodless glomeruli. Such glomeruli are composed more of tissue than of blood, probably because of proliferation of the cells within the glomeruli. In contrast, in acute glomerulonephritis the glomeruli appear as red dots.

The presence of petechiae in the kidney suggests several diagnoses. The glomeruli may appear as elevated red dots in acute

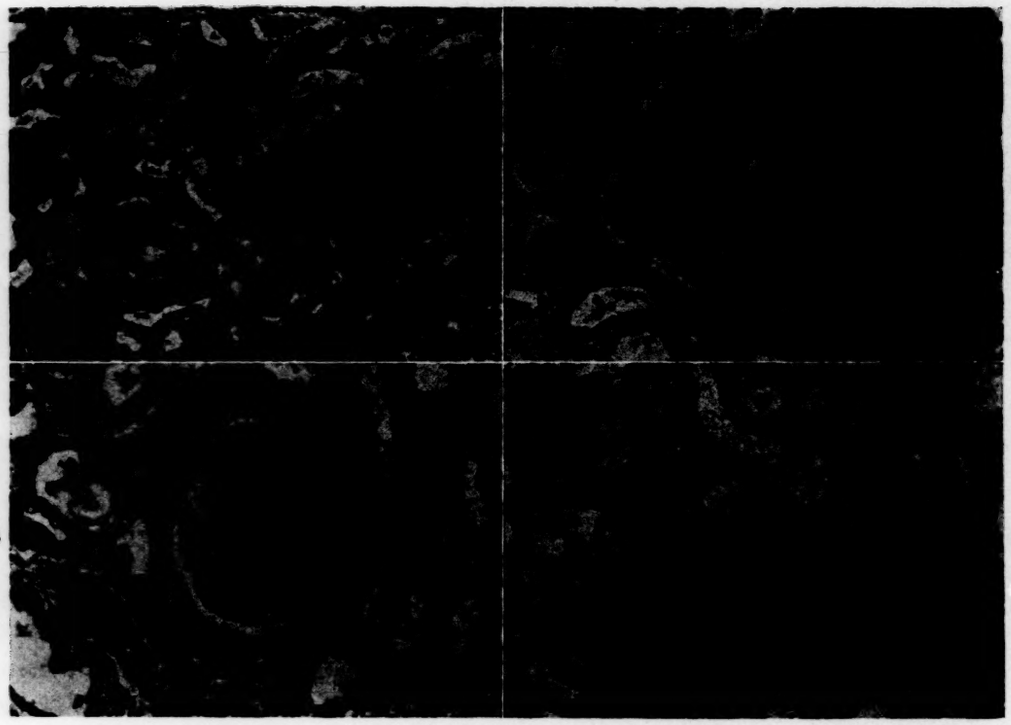

FIG. 1. Increased interstitial tissue, flattened tubular epithelium and pathologic changes in the glomeruli of the renal cortex in subacute glomerulonephritis.
FIG. 2. Detailed view of epithelial crescent in Bowman's capsule, increased fibrous interstitial tissue and altered tubular epithelium.
FIG. 3. Partially infarcted glomerulus with a lobule that has been replaced by a hyalin thrombus.
FIG. 4. A glomerulus that is almost totally obliterated and replaced by fibrous tissue; such glomeruli were rare.

glomerulonephritis because of the amount of blood within the congested and inflamed glomeruli. On the other hand, more frequently petechiae in the kidney represent hemorrhage into the glomerular capsules and into the convoluted tubules. The fact that there were such hemorrhages in the cortices of these kidneys and that there were red blood cells in the patient's urine might indicate a certain degree of activity of the nephritis in contrast with a more chronic lesion.

In the heart the valves were essentially normal. The heart was increased in size and weight. Therefore, some explanation for the hypertrophy of the heart other than valvular disease or a congenital anomaly must be sought. As for the possibility of bacterial vegetations disappearing, I do not know whether that is possible. I have seen rather small vegetations which were apparently healed in hearts of patients who had received extensive treatment five or six months before death, but there was still no question at necropsy that vegetations were present. In such cases although the lesions were very small, there was still some cellular activity; in this case I do not think that a vegetation could have healed to the point at which it was no longer evident in such a short time. There was no evidence of rheumatic fever; we made a number of sections of the myocardium and found no Aschoff bodies in any of the sections.

Figure 1 illustrates a characteristic microscopic field of the renal cortex in which the pathologic changes are diffuse and of fairly uniform intensity. There is a definite increase in the amount of interstitial tissue and an alteration in the type of the tubular epithelium, both of which changes indicate a disease of considerable duration. In addition every glomerulus is involved. The following sections illustrate the changes in

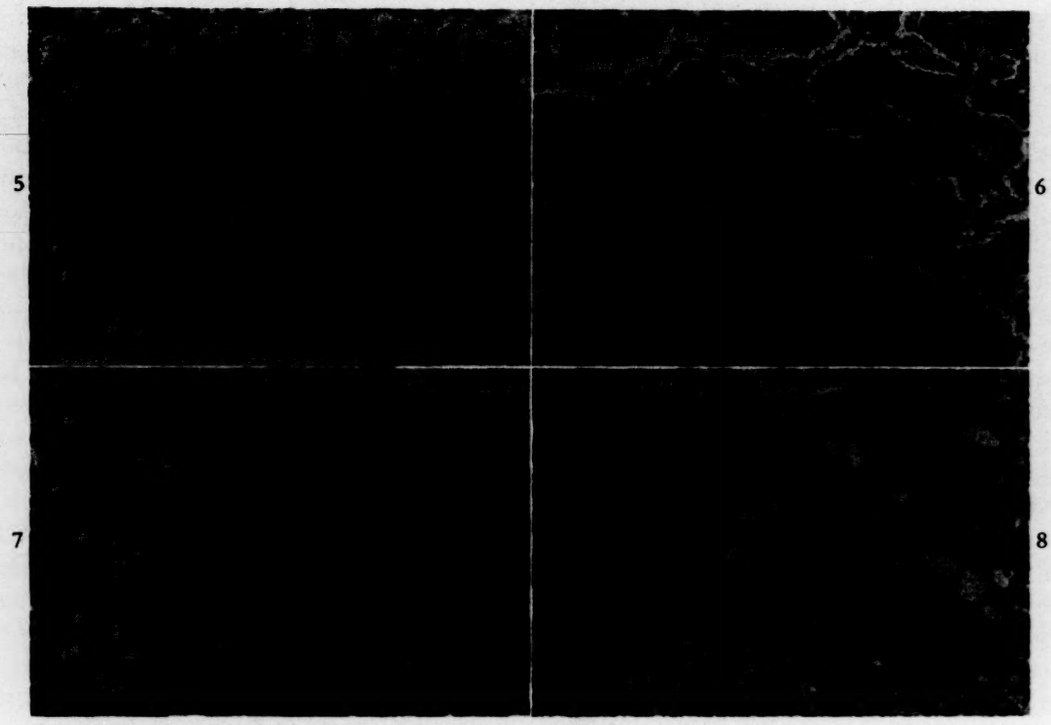

FIG. 5. Hemorrhage into a glomerular space with filling of the proximal convoluted tubule; these lesions had the gross appearance of petechiae in the renal cortex.
FIG. 6. Hemorrhage and edema in the lungs with no significant inflammation.
FIG. 7. Fibrinous pericarditis of the type that typically occurs in uremia.
FIG. 8. Increased numbers of transitional clear cells in the parathyroid indicative of secondary hyperplasia.

greater detail: In Figure 2 there is a glomerulus with epithelial proliferation and formation of a large crescent in Bowman's capsule which is typical of subacute glomerulonephritis. There is also a distinct increase in interstitial connective tissue and alteration of the cellular type in the proximal tubules to a flattened type of cell that does not have the appearance characteristic of cells of the normal proximal convoluted tubules. In Figure 3 a large part of the glomerulus has been totally lost as if it had been infarcted and the destroyed lobule had been replaced by a hyalin thrombus. There are a few infarcted glomeruli throughout these sections and I think that one may relate them to changes in the entering arterioles. This patient developed a minor degree of the malignant phase of vascular disease with necrosis of the arteriolar walls and resultant infarction of individual glomeruli; necrosis is not a prominent part of the total picture. Figure 4 illustrates an almost totally obliterated glomerulus. There are not many such glomeruli such as is characteristic of chronic glomerulonephritis. In Figure 5 there is a nephron in which there is hemorrhage into the glomerular space; the proximal tubule connected with that glomerulus is filled with fibrin and blood. Whole blood rather than red cells alone has been poured into the glomerular space; this finding supports the concept that there was some degree of the malignant form of vascular disease in this kidney. In acute glomerulonephritis only red blood cells are present in this situation.

In a representative section of the lungs (Fig. 6) there are many alveoli filled with erythrocytes and fibrin. Here again whole blood has been poured into the bronchopulmonary spaces. There are a few polymorphonuclear leukocytes but not sufficient numbers to establish a diagnosis of pneumonia. A stain for bacteria shows no bacteria in relation to any of those leuko-

cytes so we believe that the change in the lung is one of edema, congestion and hemorrhage rather than that of an inflammatory disease such as bronchopneumonia.

A section of the pericardium (Fig. 7) shows fibrinous pericarditis typical of that seen in uremia. There is little thickening or other change in the pericardium itself. Beneath the surface there is a little edema and the few cells present are mononuclears; on the surface a large amount of fibrin has accumulated and been whipped up into irregular mounds. The fibrin does not contain any cells. This process is an inflammatory one in which there is response by fibrin and fluid but practically no response by cellular elements. It is quite different from the pericarditis due to rheumatic fever or a pyogenic infection.

In Figure 8 a section of a parathyroid gland shows a very definite increase in the number of transitional clear cells. The normal chief cell in the parathyroid gland has definitely eosinophilic cytoplasm and contains a good deal of protein. In this section many of the cells are lacking cytoplasm and the nucleus appears to be located in the center of a clear space surrounded by a prominent cell wall. This change indicates secondary hyperplasia and suggests that the patient had a renal lesion for a significant period of time; judging from the size of the tissue, however, the change was not of sufficient duration to produce distinct hypertrophy of the parathyroid gland as a whole.

These anatomic observations do not explain the tender mass which was palpated by the clinicians below the left costal border. The kidneys were not that much enlarged and the spleen at the time of autopsy, about three or four weeks after the mass was felt, weighed only 100 gm. and was bound to the diaphragm by dense fibrous adhesions. There were no infarcts in either the spleen or the kidney to explain the pain in the left upper quadrant. The only thing I can suggest is that this man had pleurisy on both sides which was at one time more advanced than it was at the time of death; it might have given origin to pain and the friction rub which were so low in the thorax that they seemed to originate below his diaphragm.

Final Anatomic Diagnoses: Subacute glomerulonephritis; serofibrinous pericarditis; congestion of the lungs, advanced, with hemorrhages into the alveoli; sanguineofibrinous pleurisy, bilateral; hyperplasia of the clear cells of the parathyroids.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Perforation of Esophageal Ulcers in Bulbar Poliomyelitis*

Report of Two Fatal Cases

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DURING the summer of 1948 in an epidemic of poliomyelitis in one section of southern New Jersey a unique form of the disease was encountered. During this epidemic a disproportionately large number of young adults were stricken with the malady, and an unusually severe form of bulbar type poliomyelitis was prominent. Table 1 represents a case tabulation of the entire group seen during this epidemic. Of very great interest was the occurrence of multiple ulcerations of the esophagus with perforation which occurred and were demonstrated at postmortem examination in two young adults.

TABLE 1

CASE AND MORTALITY INCIDENCE DURING A POLIOMYELITIS EPIDEMIC IN ONE SECTION OF SOUTHERN NEW JERSEY DURING SUMMER OF 1948

Type of Case	No. of Cases	Sex		Race		Age Range	Deaths
		Male	Female	Colored	White		
Acute anterior poliomyelitis without bulbar involvement	27 (81.9%)	18 (54.6%)	9 (27.3%)	3	24	7 mo. to 56 yr.	1 (3.7%)
Acute anterior poliomyelitis with complicating bulbar involvement	6 (1.8%)	4 (12.1%)	2 (6%)	0	6	9 yr. to 27 yr.	5 (83.3%)
Total	33	22	11	3	30 (90%)		6 (18.1%)

A review of the English literature reveals that ulceration of the gastrointestinal tract occurring as a complication of poliomyelitis was reported for the first time in October, 1948.[16] Prior to this Dublin and Larson[1] as well as Saphir[2] reported finding lymphoid hyperplasia in Peyer's patches, and foci of necrosis in the germinal centers of the mesenteric lymph nodes in careful autopsies performed on patients who died of poliomyelitis. No actual ulceration of the gastrointestinal tract was observed, however, and the lymphoid hyperplasia which did occur was *not* present in the three oldest patients of Saphir's series, i.e., ages twenty, twenty-three and twenty-eight years, respectively.

Spontaneous rupture of the esophagus has been reported many times[3–5,13,15] and has been of diverse etiology, including cases following crushing abdominal injuries,[6,7] cases occurring during defecation[8] and

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during convulsions.[9] Interestingly enough in the light of our experience with one of our cases reported herein twenty-three of thirty-five cases reported by Ridgway and Duncan in 1937 had the rupture preceded by vomiting. However, "spontaneous" rupture of the esophagus is not considered to be a case in point. Moreover, the factors commonly cited as of etiologic significance in the production of alimentary ulceration, including foreign bodies, tumors, aneurysms, corrosive agents, toxins, arterial spasm and heredity may be considered as either absent or, at most, of equivocal significance in these two cases. We believe the esophageal perforation in the cases herein recorded followed the advent of an acute peptic ulcer. The microscopic picture as interpreted by Dr. F. W. Konzelmann, pathologist at this hospital, supports this view.

This dramatic finding of esophageal ulceration with perforation is certainly more than mere happenstance, especially in view of the similar gastrointestinal tract lesions reported by Heyde and Robinson as having occurred in the stomach and duodenum in their two patients with bulbar poliomyelitis. The lesions in our patients differ inasmuch as they were situated in the esophagus. Nevertheless, the point to be emphasized is that gastrointestinal tract ulceration is a complication to be looked for and reckoned with in the care of these patients.

CASE REPORTS

CASE I. Patient B. B., a twenty year old white female stenographer, was admitted to the hospital on August 8, 1948, with a history of swimming in the rain on August 1st, during which time she became chilled. On the following day, the patient complained of backache which she attributed to unusually heavy typing duties. She became progressively worse and on August 5th had difficulty swallowing. The next day she was too ill to go to work, could not swallow solids and during the same evening she became quite weak and developed a severe headache for which she was treated by her physician. The weakness progressed until the afternoon of August 8th when she was unable to stand. At this time she was admitted to our hospital. In the past personal history there had been no serious illness, operation or accident.

On admission the patient was found to have marked nuchal rigidity as well as a positive Kernig's sign. Brudzinski's sign was negative and the Babinski and Hoffmann reflexes were absent. There was no ankle clonus. The patient could weakly extend, flex, adduct or abduct her arms but had lost the ability to pronate or supinate. She was unable to sit up and had lost the ability to adduct and abduct the lower extremities. Respirations were mostly diaphragmatic with but very weak and shallow excursions of her chest. Respiratory rate was 28 per minute, pulse rate 110 per minute and temperature 39°C. Swallowing function was weak.

Shortly after examining the patient and before a spinal tap could be done rapid paralysis of the diaphragm and of the remaining intercostal muscles ensued. She became cyanotic and was immediately placed in a respirator. The respiratory rate was fixed at 16 per minute. Between 15 to 18 cm. of water, negative pressure, and 5 to 10 cm. of water, positive pressure, were employed in the respirator.

From August 8th to August 14th prostigmine hydrobromide was administered intramuscularly three times daily in doses of 15 mg. From August 9th until death, penicillin (crystalline G, aqueous solution) was administered intramuscularly every four hours in doses of 40,000 Oxford units.

Laboratory findings were non-contributory, with the exception of an elevation of the leukocyte count which on August 9th was 17, 150 cells/mm.^{3} total; polymorphonuclear cells, 79 per cent; non-filamented, 45; filamented cells, 34; lymphocytes, 9 per cent; monocytes, 12 per cent and no abnormal cells. When repeated on August 16th, the total leukocyte count was 24,850 with 73 per cent polymorphnuclear cells; non-filamented, 42; filamented cells, 31; lymphocytes, 23 per cent; monocytes, 3 per cent and eosinophils, 1 per cent.

The patient's condition was such that she could not be taken out of the respirator once she had been placed in it. By the day following admission loss of motor function had progressed until all that remained was the ability to weakly flex and extend the fingers. Hot packs were employed to relieve muscle spasm in the upper extremities.

Frequent aspiration by means of a lubricated

soft nasal catheter was necessary to keep the throat clear of mucus. On August 10th occasional blood-tinged return was noted and was thought to be the result of trauma from the catheter. On the same day the patient was placed in moderate Trendelenburg position and parenteral feeding was started, using 5 per cent glucose in physiologic saline solution and amino acids. Extreme difficulty in speaking developed and she became incontinent of urine. On August 12th the patient had a soft, black stool. There were periods during which she became irrational. From this date on she was intermittently sedated with barbiturates as she did not sleep without them. On August 13th mucus tinged with blood was again aspirated from the pharynx. The temperature, which had been running at 39°c., climbed to 40°c. and the pulse rate increased from 120 per minute to 150 per minute. On August 16th the patient became completely irrational and expired the following day.

Postmortem examination revealed elevation of both leaves of the diaphragm, the right dome extending up to the level of the third rib anteriorly and the left dome extending up to the third interspace anteriorly. There was about 200 cc. of clear, yellow fluid in the right pleural cavity. The viscera were removed *en masse*. Patchy areas of atelectasis were noted in the lower lobes of both lungs. The heart exhibited a healed rheumatic endocarditis. A ragged perforation of the esophagus, measuring 2 by 1 cm., was found on the posterior wall just below the juncture of the middle and lower thirds. The mediastinum in the region of the perforation contained about 10 cc. of dark brown material. This same material stained the edges of the perforation and formed the contents of the esophagus, stomach and upper small intestine. Two shallow ulcerations were also noted on the posterior wall just above the juncture of the middle and lower thirds of the esophagus. The gastric mucosa was grossly normal. No lymphoid hyperplasia was noted. There was a marked congestion of blood vessels of the brain and spinal cord, and marked reddening of the anterior horn regions throughout the length of the cord. Scattered petechial hemorrhages were noted in the cerebral white matter.

Microscopic examination revealed atelectasis and bronchopneumonia in the lungs. The shallow esophageal ulcers exhibited loss of stratified squamous epithelium with necrosis and mild inflammatory reaction in the exposed submucosal tissue. A section through the edge of the perforation showed complete loss of tissue down to the smooth muscle coat with superficial necrosis of the smooth muscle. There was little or no inflammatory reaction. The necrosis was of the type that would be produced by autolytic digestion. Sections through several regions of the spinal cord revealed severe degeneration of the gray matter throughout its length. Both anterior and posterior horns were involved. Only occasional anterior horn cells were seen and these exhibited various stages of degeneration. There was perivascular round cell infiltration and a similar infiltration of the leptomeninges. There were small hemorrhages around blood vessels. The entire picture was one of degeneration with little proliferation.

Case II. Patient, H. O., a twenty-seven year old white male, became ill with coryza, nausea and vomiting on September 30, 1948. He was seen on the same day by his physician who told him he had an elevated temperature and gave him a prescription of unknown content. This medication did not help him and on October 3rd he noticed difficulty in getting out of bed; three days later he was unable to sit up. He called in another physician who immediately sent him to the hospital. His past medical history was non-contributory.

Physical examination on admission revealed an acutely ill young man whose speech was slurred, but not nasal, in quality. He complained of diplopia and had a small vertical, irregular nystagmus which was especially noticeable when viewing the fundus. The fundus itself was negative except for somewhat engorged veins. The internal rectus muscle of the left eye was weak. He had a small, discrete punctate keratitis of the right cornea. In the lower extremities nearly complete paralysis of the extensors, adductors and abductors of the legs and dorsiflexors of the feet was noted bilaterally. The flexors of the legs and plantar flexors of the feet were weak but not nearly to the extent of the other groups. The patient was able to flex his arms weakly but had lost the power of extension. Pronation and supination, adduction and abduction of the arms were impaired as was the ability to hunch his shoulders. He was unable to sit up by himself, and when held in the sitting position he found it difficult to hold his head erect. Tenderness but no rigidity was elicited on flexion of the neck. Both the Kernig and Brudzinski signs were negative. Hyporeflexia was noticed in the

lower extremities, with absent cremasteric and abdominal reflexes. He was able to drink water from a glass by means of a straw and examination revealed his gag reflex to be intact. The respirations were observed to be purely abdominal and his respiratory rate to be 28 per minute. The lungs were found to be physiologic, as was the heart. The pulse rate was 100 per minute. The blood pressure 170/100 mm. of mercury, temperature 39.2°C.

Prostigmine hydrobromide was administered intramuscularly in doses of 15 mg. every six hours for a total of six doses. In addition, penicillin was administered in doses of 300,000 units daily to aid in combating patient's extremely toxic state. The patient became irrational during the next twenty-four hours. However, the nurses were able to give him some fluids by mouth up until 9:00 P.M., on October 7th. During the day he had complained of abdominal pain and had become incontinent of feces and urine. (The feces were light brown in color.) It was necessary to aspirate the pharynx by means of a soft, lubricated nasal catheter. On October 8th at 12:15 A.M. the patient became suddenly worse. His nail beds and lips developed a cyanotic tinge and there were frequent twitchings of the corners of his mouth. The respirations increased to 38 per minute and were observed to be shallow and purely abdominal. The house officer on duty placed the patient in a respirator with the respiratory rate fixed at 16 per minute. Between 16 to 18 cm. of water, negative pressure, and 0 cm. of water, positive pressure, were employed in the respirator. His pulse rate was found to be 160 per minute. Shortly after being placed in the respirator he vomited a large quantity of coffee-ground vomitus. Immediate aspiration kept his airway clear and he was placed in the Trendelenburg position to facilitate drainage. At this time his abdomen was distended and tympanitic. One unsuccessful attempt was made to pass a Levine tube into the stomach. However, the tube passed into the trachea and at no time went more than a few cm. down the esophagus. The extremely poor condition of the patient precluded further manipulation and the procedure was abandoned. Oxygen by intranasal catheter was administered; however, the patient failed to respond and expired at 7:45 A.M. on October 8th.

The significant laboratory findings consisted of a spinal tap, urinalysis and a blood count. The initial pressure was 270 mm. H_2O with a final pressure of 135 mm. H_2O after the removal of 7 cc. of spinal fluid. Protein in the spinal fluid equalled 62 mg. per 100 cc., sugar, 40 mg. per 100 cc. and chlorides, 740 mg. per 100 cc. The total white cell count was 151 cells, 78 per cent of which were polymorphonuclear cells and 22 per cent lymphocytes.

The urine was found to contain four plus acetone but was otherwise negative. The total white cell count was elevated to 12,450 cells with a normal distribution.

Postmortem examination revealed considerable cyanosis of the head, neck, upper thorax and nail beds. The left pupil was widely dilated. There was considerable distention of the small intestines and colon. The urinary bladder was distended. The domes of the diaphragm extended up to the third anterior interspace, bilaterally. Both lungs were partially collapsed. The viscera were removed *en masse*. Congestion of the posterior portions of both lungs was noted. There was congestion of both kidneys. Upon opening the esophagus an ulcer 1.5 cm. in diameter was noted on the left posterolateral wall 3 cm. above the cardia. The ulcer had perforated into the mediastinum. The edges of the ulcer were stained with dark brown material similar to that present in the lower end of the esophagus, stomach and upper small intestines. This same material, which probably represented partially digested blood, had penetrated into the mediastinum and into the abdomen retroperitoneally through the esophageal hiatus. A moderate amount of mediastinal emphysema was present. Another ulcer, superficial and nonperforating, was noted at the juncture of the middle and lower thirds of the esophagus. A hypertrophic gastritis was present. The other viscera were grossly normal. There was no sign of lymphoid hyperplasia. Congestion of the surface blood vessels of the brain and spinal cord was present, as was injection of the anterior horn region of the spinal cord.

Microscopic examination revealed marked congestion of the kidneys. The grossly abnormal areas of lung exhibited edema, hemorrhage and foci of brownish amorphous matter representing aspirated vomitus. The remainder of the lungs was normal. A section of stomach showed congestion and hypertrophic gastritis. The edge of the esophageal perforation showed loss of epithelium, exposure of deeper layers and necrosis of all layers. The observed necrosis was of the type consistent with autolytic digestion. The shallow ulcer of the esophagus was of the

typical peptic ulcer type. The spinal cord showed perivascular round cell infiltration, degeneration of the ganglion cells of the anterior horns and glial proliferation in the anterior horns, all cardinal features of Heine-Medin's disease. Other organs showed no relevant lesions.

COMMENTS

In pondering over the possible contributory factors in the production of the esophageal ulcers in these two patients, it was concluded that regurgitation of hydrochloric acid and pepsin, with autolytic digestion, was a most likely contingency, probably acting in conjunction with other factors. Many reports in the literature tend to support this intriguing possibility.

G. Steiner[3] in a discussion of the etiologic factors concerned with the production of chronic ulcerative esophagitis, placed gastric juices high on the list of possibilities. He listed the effects of gastric juice on the esophagus as occurring in the following states: (1) ectopic gastric mucosa; (2) repeated acid vomiting; (3) regurgitation of gastric juices through an unduly patent cardia; (4) hiatal gastric hernia and (5) peptic predisposition. Although ectopic gastric mucosa was not present in the microscopic sections and hiatal hernias were not found at postmortem examinations in our two cases, any or all of the remaining states postulated by Steiner may be considered as having been present.

Bachrach, Grossman and Ivy[10] give the pH of the hydrochloric acid secreted by the parietal cells as 0.58, and discuss the resistance of the gastrointestinal tract to the digestive action of its own secretions. They also refer to the work done by Harley[11] as far back as 1860 in which he demonstrated the digestive action of gastric juices on mucosa from which the mucus had been removed. They conclude that, "the stomach does not digest itself when the circulation of its mucosa is adequate, when the tolerance of the cells to acid-pepsin is not exceeded and when the nutritional or metabolic condition of the subject is adequate for the regeneration and proliferation of the cells of the gastric mucosa and for mucus secretion." An almost diametrically opposite state of affairs existed in our cases if one permits the substitution of "esophageal" for "gastric" mucosa. Palmer[12] comments that, "it seems evident that in gastric ulcer the primary defect is probably one of decreased mucosal resistance, arising in some unknown manner." Meyer et al. concur with this viewpoint and state, "According to our hypothesis, the role of pepsin and HCl in the pathogenesis of peptic ulcer may be secondary to the removal of the surface mucus by lysozyme." The role of this enzyme in the production of alimentary ulcerative disease "is suggested by: (1) Distribution of lysozyme along the digestive tract, (of highest concentration in duodenum and pyloric regions where peptic ulcers are found most frequently). (2) Increased concentration found in alimentary ulcerative disease. (3) Removal of surface mucus by the enzyme. (4) Production of ulcerative lesions by oral administration of crystalline lysozyme."

In the further development of the thought that regurgitated hydrochloric acid was of etiologic significance, the recumbent and Trendelenburg positions in which these two patients were obliged to remain for many hours are considered to have been of definite contributory significance. This attitude would, of course, serve to facilitate the reflux of hydrochloric acid from the stomach into the esophagus by gravity. Additional corroboratory evidence in this regard is the fact that the ulceration in both cases occurred in the posterior or posterolateral walls. These regions are, of course, the anatomic sites where puddles of regurgitated hydrochloric acid and pepsin would accumulate.

The phrenic nerve paralysis which both of these patients experienced resulted in marked elevation of both hemidiaphragms and served to relax the cardia, further facilitating regurgitation of the stomach contents into the esophagus through "loss of the pinchcock-action of the crura," (Steiner).[3]

The possible effects of other contributory

factors is recognized. With the present day concepts of "psyche and soma," the consideration of psychosomatic features is certainly in order when thinking in terms of the etiologic factors of gastrointestinal tract ulceration. Both of these young adults experienced profound fear with the realization they had poliomyelitis and were sick enough to require respirators, and it is conceded that this fact influenced their course unfavorably in many respects. However, we believe that the psychosomatic influence in the production of ulcers is of importance only in the prolonged, chronic, emotional states. The very acuteness in the above described cases minimizes the part played by any concomitant psychiatric disturbances.

Trauma due to postoperative suction tubes was stressed by Paul in 1943; and although aspiration was carried out in both cases, it was performed by one of the authors (H. McD.) who at no time went below the hypopharynx with the aspirating tube. There is equal certainty that in the one attempt at intubation in the second case, the Levine tube did not at any time descend below the upper one-third of the esophagus. Yet the most cephalad ulceration was found just above the juncture of the middle and lower thirds of the esophagus while the perforated ulcers were at, or below, this site. Trauma due to intubation may be eliminated as a possible etiologic factor in the above reported cases. Conceivably, however, the mechanical action of the respirator could produce trauma through a churning back and forth in the esophagus of air and gastric contents. In an individual with absent reflex and sensory modalities such an action would certainly add to tissue surface injury, however produced. It is believed that this mechanism may well have brought about the actual perforation whether or not it contributed to the initial ulcer formation.

Although the advisability of placing these patients with bulbar-type poliomyelitis in respirators may be questioned in view of the current recommendations of the National Poliomyelitis Foundation, at the time it seemed to be the treatment of choice. The first patient was placed in a respirator prior to the onset of bulbar symptoms and could not be persuaded to remain out thereafter. The second patient became suddenly worse shortly after midnight and was placed in a respirator by a house officer. He progressed very rapidly downhill and, as recorded above, expired early the next morning.

Apropos of the toxins produced in this condition, one may only comment that the toxins produced in poliomyelitis are predominantly those which are neurotropic. None has been demonstrated which has an ulcerative effect on the gastrointestinal tract mucosa. The significance of any elaborated toxins probably lay in their contribution to the generalized debility of the patients, rather than in any specific harmful effect limited to the mucosa.

Ingested organisms are censured on many accounts, not the least of which is their possible contribution to the etiology of peptic ulcers. Any organisms, ingested by the above two patients, played an undeterminable role in the formation of their ulcers. As stated by Tileston,[4] swallowing of organisms is of most importance in the presence of inflammation. This usually occurs during the course of acute inflammatory disease, e. g., pneumococcal pneumonia, diphtheria, streptococcal and staphylococcal infections. Of necessity this factor is of no more than conjecture in the above described instances of ulcer formation.

From the preceding considerations it is superfluous to say one cannot be dogmatic about the etiology of the ulceration with perforation in the cases presented. Undoubtedly, several factors played a part. We believe, however, that the mechanism as postulated for the formation of these ulcers, as peptic ulcers of the esophagus, is a most reasonable contention. It is on this basis that several therapeutic recommendations are proffered with the hope of obviating or, at least, minimizing the future occurrence of this complication.

1. Antacids, to neutralize the acid content of any regurgitated stomach contents, in conjunction with a bland diet, should be

administered to all patients who are required to spend protracted periods in a respirator and who are able to swallow. Probably a modified Sippy diet would be the ideal regimen. Rectal and intravenous feeding should be started early in patients unable to swallow in an attempt to maintain tissue resistance and combat debility.

2. Semi-Fowler or upright positions should be employed whenever possible.

3. Tracheotomy with O_2 by catheter should be considered early. Placing of patients with bulbar-type polio in respirators should be done as a last resort only. If bulbar symptoms develop, those patients already in a respirator should be removed if possible.

4. Chemotherapy should be employed both prophylactically and therapeutically in patients with bulbar-type poliomyelitis. In the presence of a mediastinitis consequent to perforation, medical rather than surgical handling is almost imperative in these cases.

SUMMARY

1. Two fatal cases of bulbar-type poliomyelitis with complicating perforation of esophageal ulcerations are presented.

2. Possible etiologic factors are discussed and arguments advanced for the theory that the ulcerations were peptic in origin. It is believed they were produced by regurgitation of stomach contents into the esophagus which, associated with other factors, brought about autolytic digestion. These other factors are discussed.

3. Various prophylactic and therapeutic measures are suggested.

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Familial Hemorrhagic Telangiectasia with Associated Pulmonary Arteriovenous Aneurysm*

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In recent medical literature there is evidence of increasing interest in the subject of pulmonary aneurysms, particularly arteriovenous aneurysms. Long considered a rarity, this condition is being reported more frequently as one of the causes of polycythemia and one which sometimes is amenable to surgical treatment.

In case reports of pulmonary arteriovenous aneurysms there have been occasional references to the association of skin telangiectasia, and the opinion has been expressed that very probably some of these patients had the disease "familial hemorrhagic telangiectasia" (Rendu-Osler-Weber disease) even though they had not been so reported. Barnes, Fatti and Pryce[1] state that of the twenty-five arteriovenous aneurysms of the lung thus far reported in the literature, six had epistaxis and eleven had cutaneous and/or mucous membrane telangiectases. In only four instances was there unequivocal evidence of an hereditary factor although in two other cases there was presumptive evidence. In a recent review of the literature Goldman[2] was able to find reports of seventeen patients who had symptom-producing pulmonary arteriovenous aneurysms, and approximately half of these patients also had telangiectases elsewhere on the body. He reported two siblings who had pulmonary arteriovenous aneurysms but no associated telangiectasia. It was noted, however, that their grandmother had been subject to nosebleeds most of her life. Moyer[3] described two members of a family having both hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistulas.

During the past year at the University of Oregon Medical School Hospitals and Clinics three patients having pulmonary arteriovenous aneurysms have been seen. All three of them had telangiectasia and two of them gave a history of hereditary incidence sufficiently definite to warrant the diagnosis of Rendu-Osler-Weber disease. These latter two patients are reported in this paper. The third patient was successfully treated surgically by excision of the pulmonary arteriovenous aneurysm.

CASE REPORTS

Case 1. V. L., a forty-six year old laundress, was admitted to Multnomah Hospital on September 8, 1947, complaining of weakness, swelling of her ankles, nosebleeds, vomiting blood and passing blood by rectum.

She stated that her health had never been good. In childhood she had had frequent upper respiratory symptoms, mild gastrointestinal complaints and rather severe "growing pains" in the calves of her legs. At about the age of thirteen years she began having spontaneous epistaxis lasting fifteen or twenty minutes. At first her nosebleeds occurred only three to five times a year but the frequency gradually increased and by the time she was twenty-five years old epistaxis occurred several times a week and sometimes daily.

At the age of twenty-five years she had an illness characterized by chills, nausea and abdominal cramps. Her physician found signs of fluid in her left chest and he aspirated blood

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from her left thorax in an amount estimated by her to be about 1½ quarts. Convalescence from this illness was uneventful and she has had no recurrence.

Her first admission to Multnomah Hospital was on May 4, 1936. She complained then of having had "the flu" about seven weeks prior to entry. She was confined to bed for five days and following this she became progressively weaker and developed dyspnea, swelling of her legs, dry cough and a "drawing sensation" in her chest. On admission her temperature was 98.6°F., pulse 120, respirations 22 and blood pressure 130/60. Pallor was very marked. Lesions which were described as petechiae were noted on the buccal mucous membranes and on the periphery of her tongue. Neck veins were distended. Lungs were clear. The heart was thought to be somewhat enlarged and there were blowing systolic apical and tricuspid murmurs and gallop rhythm described. The liver was markedly enlarged and "a splenic mass could not be separated from the huge left lobe of the liver." There was edema of both lower extremities. The blood count on her first admission showed hemoglobin 19.6 per cent (2.68 gm.), red blood cells 1,360,000, color index 0.7, white blood cells 7,500 with normal differential, and platelets 138,000. Urine was negative except for 1 plus albumin, and serology was negative. X-ray of the chest was reported as follows: "On the left side, lying opposite the 7th and 8th ribs in the posterior axillary line, there is a hazy increased density, which appears to be within the lung field or in the pleura. This is rather sharply outlined; it does not appear to be a pneumonic process; it has more the appearance of a tumor. Cardiac shadow is moderately enlarged both to the right and to the left and has no typical configuration." An electrocardiogram was normal.

The patient responded well to multiple transfusions and iron therapy although she had three episodes of epistaxis while in the hospital and she was still moderately anemic at the time of discharge.

At this first admission various diagnoses were considered, including rheumatic heart disease, subacute bacterial endocarditis and leukemia. However, her final diagnosis was simply "hypochromic anemia," secondary to chronic blood loss.

Following her discharge from the hospital in 1936 she did not return for further medical care until her admission in September, 1947. In the eleven-year interim her epistaxis continued about as usual. In 1942 she began to have episodes of vomiting blood and these recurred at three- to six-month intervals. They were likely to occur especially after an evening meal. Nausea would at times be followed by cramping pains in the epigastrium and after two or three hours she would induce vomiting. The first portion of the emesis was black, mixed with food particles. The last part was usually bright red blood. Following these attacks she usually noticed severe weakness and occasionally sharp pains in the upper left chest. She stated that after August, 1946, the vomiting attacks had been followed in approximately an hour by a large bowel movement consisting of "dark red blood." Her last emesis before admission had occurred in July, 1947. Following this she continued to feel very weak and had noticed slight ankle swelling. It was especially because of her weakness that she re-entered the hospital in September. She had had no dyspnea. Appetite had remained good and she had not lost weight. Menses had stopped in 1942.

Her family history is of interest in that her mother had nosebleeds every day for as long as the patient could remember and she eventually "bled to death" at the age of fifty. The patient's sister also had very frequent nosebleeds all her life and according to the patient the sister also had bluish lesions on her lips similar to those of the patient.

On physical examination in September, 1947, her temperature was 98.4°F., pulse 84, respirations 22 and blood pressure 90/50. She was normally developed but thin and quite pale. On the tongue and lips there were multiple purplish telangiectatic lesions. (Fig. 1.) Examination of the nasal passages, nasopharynx and larynx revealed no telangiectases but a few were found on the pads of her fingers and one beneath a fingernail. Most of the lesions were minute and not appreciably raised above the surface; however, one of the lesions on the tongue was 3 mm. in diameter and was raised above the surface in what appeared to be a tuft of small venules. Her thyroid was palpable but not enlarged; her chest was thin, symmetrical and resonant throughout. A few medium resonant rales were heard at both bases posteriorly. The cardiac apex was percussed just outside the mid-clavicular line in the fifth interspace. At the apex there was heard a rough systolic

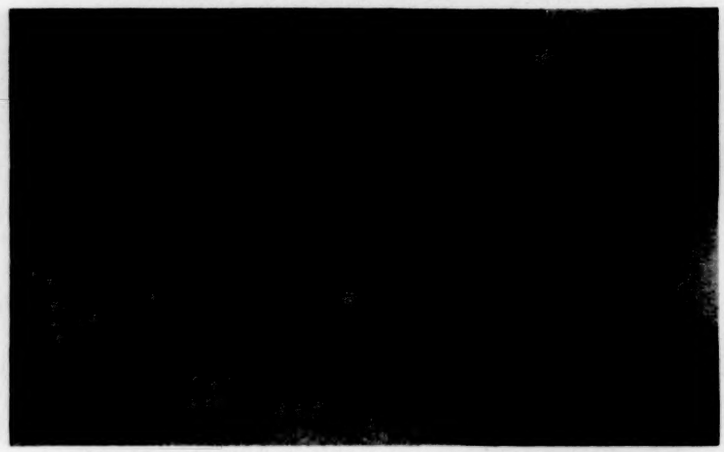

FIG. 1. Infra-red photograph of telangiectases on the tongue and lips of Case 1.

murmur of grade 2 intensity and a fainter early diastolic murmur. With the patient in a sitting position both murmurs were accentuated, and particularly the diastolic component was more easily heard and seemed to be a continuation of the systolic murmur, extending through the second sound well into mid-diastole and giving the effect almost of a continuous murmur. Very striking was the marked increase in intensity of the murmur at the end of deep inspiration. The liver was palpable 4 cm. below the costal margin in the mid-clavicular line, and the spleen was palpable 3 cm. below the left costal margin on deep inspiration. There was pitting edema over the sacrum and slight edema of both lower extremities below the mid-tibial region. There was no clubbing of the fingers. On admission no cyanosis was noted.

Laboratory data: Hemoglobin 61 per cent (8.4 gm.), red blood cells 3,900,000, color index 0.76, white blood cells 6,800, polymorphonuclear neutrophiles 80 per cent, lymphocytes 18 per cent, eosinophiles 1 per cent, monocytes 1 per cent, disintegrated cells 3 per cent. Slight achromia and variation of size and shape of red blood cells were noted. Icterus index 10, sedimentation rate 3 mm. in 15 minutes and 21 mm. in 45 minutes (modified Westergren method). Red blood cell fragility: hemolysis began in 0.44 per cent and was complete in 0.30 per cent NaCl; platelet count 85,000 (accuracy questioned). Clot retraction began at one hour and was complete at 7 hours; coagulation time 6 minutes (Lee and White); prothrombin time 83 per cent of control; Rumpel-Leede test negative. Bromsulfalein liver function: less than 1 per cent retention at 20 and 45 minutes. Cephalin-flocculation test negative. Total serum proteins 6.7 per cent, albumin 4.1 per cent, globulin 2.6 per cent; Kolmer negative, urinalysis normal. Examination of sternal marrow showed only the changes compatible with an anemia of chronic blood loss.

Sigmoidoscopy to 20 cm. showed no bleeding points, telangiectasia or other abnormalities. X-ray study of esophagus and stomach revealed no evidence of esophageal varices or of peptic ulcer and the appearance of stomach and duodenum was normal.

Gastroscopy was done by Dr. George Long. Care was taken to examine the mucosa before inflation of the stomach with air in order to avoid production of hemorrhagic lesions by such trauma. About ten sharply demarcated red lesions were visualized scattered throughout the stomach. The lesions appeared to be sub-mucosal and were estimated to be from 1 to 4 mm. in diameter. They did not appear to be elevated and the edges were not "star-shaped." They were either oval or round with smooth borders. None of the lesions showed evidence of bleeding at the time of the examination. (Fig. 2.)

Her electrocardiogram was within normal limits. X-ray of the chest (Fig. 3) showed some straightening of the left cardiac border. The heart otherwise appeared normal in size and configuration. The right lung field appeared clear. There were two markedly enlarged vascular shadows extending from the left hilum down into the left base. They appeared to merge with a vague rounded density which partially overlay the cardiac apex. On cardiac fluoroscopy none

of the cardiac chambers seemed enlarged. The oval density in the left lower lung field was seen to demonstrate expansile pulsation. It was interpreted as probably representing an aneurysm of a pulmonary artery branch or an arteriovenous aneurysm. Angiocardiograms were then taken, using 50 cc. of 70 per cent diodrast. The first film (Fig. 4) taken approximately two seconds after onset of injection of the diodrast showed filling of the superior vena cava, right auricle and ventricle and pulmonary arteries. The density in the left lower lung field was simultaneously opacified with the pulmonary arteries. It was seen to be connected to several dilated vascular channels. The vessels entering the mass appeared considerably more prominent than those on the opposite side. The arterial branches leading to the mass were accompanied by parallel venous branches, which could be clearly identified and also contained diodrast. These x-ray studies seemed quite definitely to establish the pulmonary lesion as an arteriovenous aneurysm.

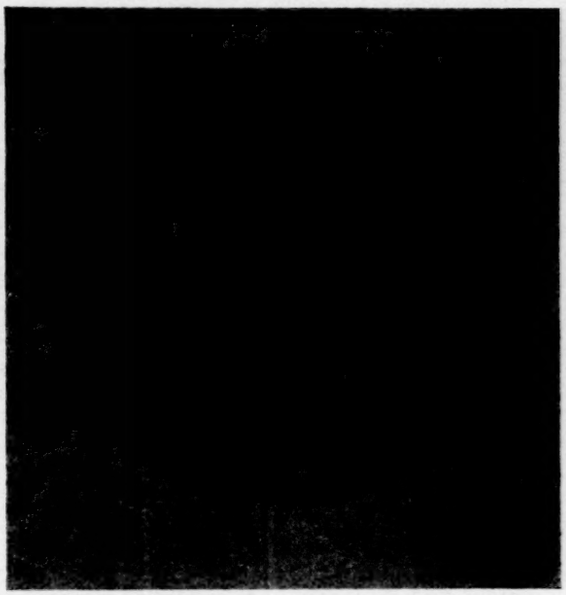

FIG. 2. Photograph of a drawing of a telangiectasis of the gastric mucosa as seen on gastroscopic examination of Case 1.

FIG. 3. Postero-anterior x-ray of the chest of Case 1 showing two enlarged vascular shadows extending from the left hilum down into the left base where they appear to merge with a vague rounded density in the region of the cardiac apex.

FIG. 4. Angiocardiogram of Case 1 showing opacification of the superior vena cava, right auricle and ventricle, pulmonary arteries and dilated vascular channels entering an aneurysm.

Further evidence of arteriovenous shunt was afforded by oxygen determinations on arterial and venous blood, the arterial saturation showing lower than normal values on two occasions, both early in her hospitalization while she was anemic and again later after her blood count had returned to normal. Blood oxygen content determinations were done by the acid ferricyanide method in the Van Slyke manometer, and oxygen capacity by saturation with 100 per cent oxygen at room temperature in a Bancroft tonometer. The following values were obtained:

September, 1947

Arterial blood sample:	
Oxygen capacity...	12.95 vol. % (9.29 gm. hb./100 cc.)
Oxygen content....	11.25 vol. %
Oxygen saturation..	86.8%
Venous blood sample:	
Oxygen content....	8.58 vol. %
Oxygen saturation..	66.3%

March 6, 1948

Arterial blood sample:	
Oxygen capacity...	18.92 vol. % (13.8 gm. hb./100 cc.)
Oxygen content....	15.6 vol. %
Oxygen saturation..	82.5%
Venous blood sample:	
Oxygen content....	9.29 vol. %
Oxygen saturation..	49.1%

The patient remained in the hospital for ten days in September. She received three transfusions without reaction. Her hemoglobin at time of discharge was 97 per cent (13.4 gm.) and it was noted that with this rise in her hemoglobin a mild but definite cyanosis had appeared. Her edema had completely subsided and she was asymptomatic. She was given 20 mg. of rutin three times a day and ferrous sulfate 0.3 gm. three times a day, and has remained relatively well since discharge. She has continued to have occasional epistaxis but has had no gastrointestinal bleeding and her blood count has shown a tendency to increase above the average normal, the count on March 6, 1948, showing 118 per cent (16.3 gm.) hemoglobin and 5,500,000 red blood cells. Her platelet count on this same date was 307,000 and her circulation time was 14 seconds (arm to tongue-decholin) and 7.5 seconds (arm to lung-ether). Her vital capacity was 2.6 l. or 80 per cent of normal. A chest x-ray showed no change compared to her previous examination. Blood pressure has remained rather low, 88/60 right, 100/68 left. A subsequent blood count on April 27, 1948, showed 122 per cent (16.8 gm.) hemoglobin and 6,600,000 red blood cells. At this time her cyanosis was quite marked.

Comment. This case exhibits remarkable similarity to the case of pulmonary aneurysm associated with hemorrhagic telangiectasia reported by Rundles.[4] Epistaxis, gastrointestinal hemorrhage, anemia and enlargement of the liver and spleen were prominent features of his case.

Case 1 presented a variety of diagnostic problems during the period of her medical observation both from the standpoint of symptoms and of physical findings. Prominent have been her epistaxis, hematemesis, anemia, hepatomegaly, splenomegaly and the findings of a pulmonary arteriovenous aneurysm lying adjacent to the cardiac apex. The murmurs arising in the aneurysm, although of unusual character, were so closely associated with the cardiac sounds and the mitral area that evaluation was difficult, and it is not surprising that the diagnosis had been made at one time of rheumatic heart disease with mitral stenosis and insufficiency. Because of her findings of anemia, splenomegaly, petechial-like lesions and murmurs, a good case had also been made for subacute bacterial endocarditis.

At another time, with hematemesis her presenting symptom, the diagnosis of peptic ulcer was prominently considered. With negative gastrointestinal x-rays and because of the enlarged liver and spleen, a diagnosis had been made of cirrhosis of the liver with bleeding esophageal varices. Liver function tests, however, were normal.

It has been assumed that gastrointestinal hemorrhage is a fairly common occurrence in hemorrhagic telangiectasia. However, Gambill[5] states that of the thirty-one cases of hereditary hemorrhagic telangiectasia recognized at the Mayo Clinic from 1920 to 1944 inclusive, none gave a history of gross gastrointestinal hemorrhage.

Rather interesting is the fact that her pulmonary arteriovenous aneurysm has caused her so little trouble during the eleven-year period. Quite possibly polycythemia has not developed as a result of her pulmonary arteriovenous shunt because of the frequent bleeding from her telangiectasia. That such might be the case is suggested by the fact that with less hemorrhage during the last six months there has been a steady rise in her hemoglobin and erythrocyte count and definite cyanosis has

become clinically apparent. Whether this trend will continue or whether with increasing blood volume there will be more frequent and severe bleeding, remains to be determined.

Consideration has been given to the advisability of surgical treatment of the pulmonary aneurysm. Because of its relative benignity to date and because most of her symptoms have seemed related to other manifestations of her telangiectasia, it has been thought best not to recommend surgical treatment at this time. The use of rutin in the treatment of this case was suggested by the rather dramatic results reported by Kushlan[6] in a case of gastric bleeding proven by gastroscopy. Evaluation of the effect of rutin in the case reported here cannot be made at the present time, although gastrointestinal bleeding has not occurred during the seven months she was followed on rutin therapy.

CASE II. M. F., a sixty-six year old Irish widow, appeared at the University of Oregon Medical School Outpatient Clinic in March, 1948, where she was sent when the Chest Survey Center reported that her photofluoroscopic chest x-ray was abnormal. She had been quite well as a child except for frequent fainting spells but at the age of fifteen she began having severe left-sided headaches accompanied by nausea and vomiting. The frequency of these headaches had been much less since about 1938. Her mother had similar headaches, diagnosed as migraine. When she was about fifteen or sixteen years old she began to notice excessive shortness of breath on exertion and since then this symptom has become progressively more distressing. As a girl she felt her color was good but since the age of about twenty-five she had noticed her complexion was pale and bluish and that her lips were quite blue.

She could not date the onset of epistaxis but by the time she was thirty-one years old she was having spontaneous nosebleeds at least once a week. These had become more frequent and for the past ten or twelve years she had had epistaxis from three or four times a week to three or four times a day. At the time of her studies in the Outpatient Clinic she had not had epistaxis for one month. She had not noticed the bluish red spots on her lips, tongue, face and fingers until they were pointed out to her in the Clinic, except for one red streak beneath her right second fingernail which she had noticed for the past three or four years. About 1940 she began having distress from gas and in 1943, following five months of epigastric pain relieved by food and alkali, barium x-ray studies showed the duodenal bulb to be irritable and deformed at its inferior surface. At that time her hemoglobin was 87 per cent (10.1 gm.) and red blood cells 4,800,000. Her symptoms subsided on ulcer management. She was given iron at that time and took it for about one year. Since then she thinks her stools have all been tarry black. Since 1943 she had had frequent palpitation and feelings that "blood had difficulty getting into the heart." She described this as substernal pressure accompanied by a sensation of faintness. Occasionally she had had sharp, precordial pain not associated with exertion.

The only significant family history was in regard to the father who had frequent severe epistaxis for as long as the patient could remember. There were multiple reddish blue spots about his nose and cheeks. His complexion was bluish rather than pale. Apparently no other member of the family had epistaxis or telangiectasia. She had had a cholecystectomy and appendectomy in 1935 and a right inguinal hernia repair in 1939.

Physical examination revealed a slightly obese, well developed white female. Her temperature was 98.0°F., pulse 72, respirations 30, blood pressure 130/80. Her lips were bluish and there were dilated venules about the nose. There were multiple red maculopapular lesions which blanched on pressure, averaging 1 to 2 mm. in diameter on the cheeks, chin, lips, tongue, nasal mucous membranes, pads of the fingers and under the fingernails and toenails. (Figs. 5, 6 and 7.) Cherry angiomas were scattered over the skin of the chest and back. There was a papilloma of the skin of the back at the level of the right fifth interspace 6 cm. from the spine. There was early clubbing of the fingers and the nail beds were definitely bluish in color. The chest was symmetrical and resonant with vesicular breath tones and no rales were heard. There was a blowing systolic bruit accentuated by deep inspiration heard in the right posterior axillary line at the level of the sixth interspace. Cardiac border was percussed 8 cm. to the left of the midline in the fourth interspace. There was regular sinus rhythm and no murmurs were

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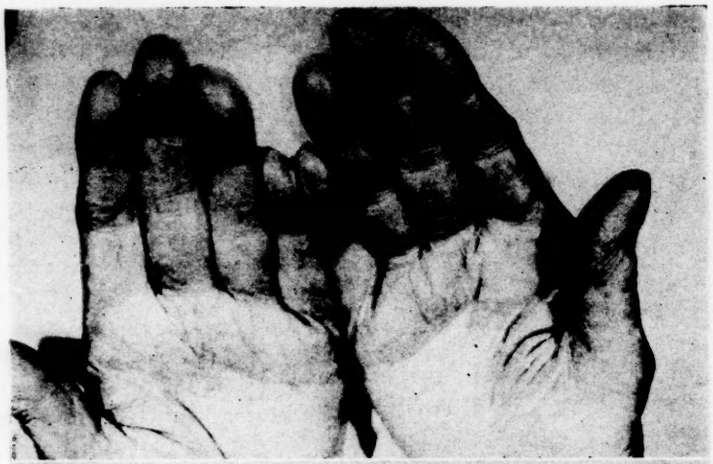

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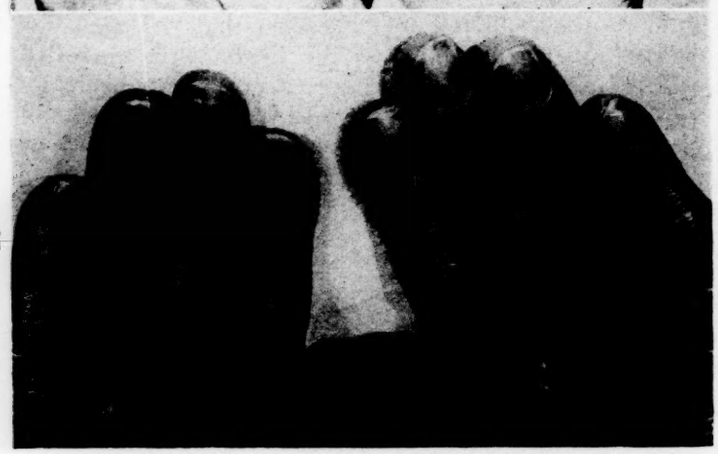

FIG. 5. Telangiectases on the fingers of Case II.
FIG. 6. Telangiectases and early clubbing of the fingers of Case II.

FIG. 7. Telangiectases of the tongue, lips, chin and cheek of Case II.

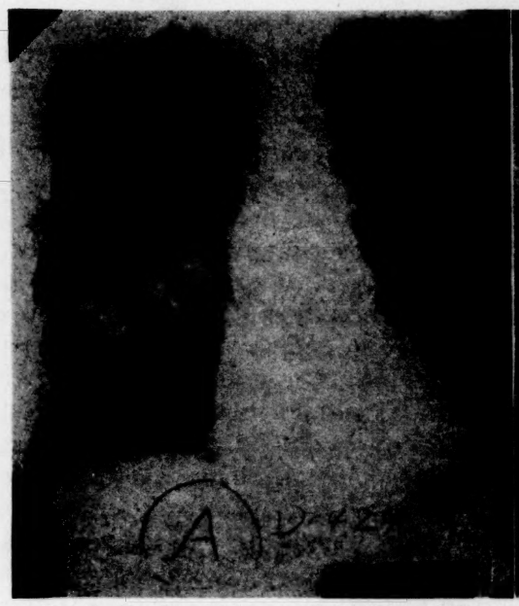

FIG. 8. Cardioangiogram of the chest of Case II in the postero-anterior projection showing the arteriovenous aneurysm and associated enlargement of vascular shadows; heart was of normal size and configuration.

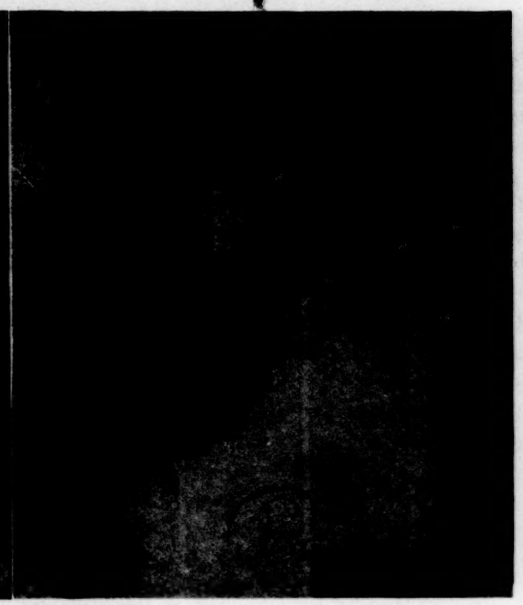

FIG. 9. Cardioangiogram of the chest of Case II in the right lateral projection, showing that the arteriovenous aneurysm lies in the apex of the right lower lobe.

heard. There was a right upper mid-rectus scar with diastasis and a right inguinal surgical scar. Reflexes were symmetrical. Pelvic examination revealed mild cystocele and rectocele and senile vaginitis.

Laboratory data: Hemoglobin 111 per cent (15.3 gm.), red blood cells 6,100,000, color index 0.88 white blood cells 6,800, polymorphonuclear neutrophiles 49 per cent, eosinophils 5 per cent, lymphocytes 39 per cent, band cells 7 per cent, disintegrated cells 3 per cent, cell volume 42.5 cc./100 cc. Blood volume 4,832 cc. (Evans blue method; weight of patient 66 kg.). Fragility of red blood cells: hemolysis began in 0.44 per cent and was complete in 0.22 per cent sodium chloride solution. Anisocytosis was present. Reticulocytes 1.8 per cent, sedimentation rate 1 mm. in 15 minutes and 60 mm. in 45 minutes (modified Westergren method), platelets 133,000, coagulation time ten minutes; clot retraction began in one hour and was complete in twenty-four hours; bleeding time three minutes, forty-five seconds. The first of four stool specimens showed 4+ occult blood, the second 3+, and the last two were negative (benzidine test). Urinalysis was normal, serology negative. Blood oxygen content determinations were done by the acid ferricyanide method in the Van Slyke manometer and oxygen capacity by saturation with 100 per cent oxygen at room temperature in a Bancroft tonometer. The following values were obtained from the studies done in April, 1948:

Arterial blood sample:
- Oxygen capacity.. 19.3 vol. % (14.0 gm. of hemoglobin/100 cc.)
- Oxygen content... 16.3 vol. %
- Oxygen saturation. 84.4%

Venous blood sample:
- Oxygen content. . 8.58 vol. %
- Oxygen saturation. 66.3%

Circulation time: Arm to lung (ether) 11 seconds;
Arm to tongue (decholin) 20 seconds.

Electrocardiogram was normal.

X-ray examination of the chest revealed the size and configuration of the heart to be within normal limits. At the level of the right hilum in the mid-lung field there was a circular density with a radiolucent area measuring 3.5 cm. in diameter. Just lateral to this were two round, soft densities, one measuring 1 cm. and the other 1.5 cm. in diameter. Remaining portions of the lung fields were essentially clear although a papilloma of the skin was visible on the x-ray plate in the region of the right axilla. Chest fluoroscopy demonstrated no enlargement of any of the heart chambers. There was a smooth-

walled, serpiginous density noted in the posterior portion of the right chest. This did not appear to have a prominent expansile pulsation but on scrutiny there sometimes appeared to be vascular movement within it. Cardioangiogram made in the postero-anterior and right lateral projections demonstrated an arteriovenous fistula in the posterior portion of the apex of the right lower lobe. (Figs. 8 and 9.)

Barium x-ray studies of the upper gastrointestinal tract showed no abnormality in the stomach or duodenum. Barium enema was done and a post-evacuation radiogram demonstrated a circular, linear density in the lower part of the sigmoid colon or upper part of the rectum. Sigmoidoscopy revealed a 5 mm. adenomatous polyp at 13 cm. and a 1 cm. polyp at 15 cm. The Proctology Department recommended resection but the patient refused surgery.

Comment. Case II represents a less unusual case of pulmonary arteriovenous aneurysm associated with hereditary hemorrhagic telangiectasia. The patient's description of her father's appearance suggests that he was cyanotic and one wonders if he might have had a pulmonary arteriovenous aneurysm. The symptoms of this sixty-six year old woman were not sufficient to bring her to a physician voluntarily although dyspnea, cyanosis and epistaxis are prominent features of the history. Here, as in Case I, it seems likely that the symptoms due to the pulmonary shunt were minimized by blood loss due to the telangiectasia. Both diagnostic studies and treatment of this case were hampered by the religious convictions of the patient.

SUMMARY

Two cases of pulmonary arteriovenous aneurysms in association with familial hemorrhagic telangiectases are reported.

In the first case, in addition to superficial telangiectasis of the skin, tongue and mucous membranes of the mouth, there were demonstrated by gastroscopy numerous telangiectatic lesions of the stomach which were thought to be the source of repeated gastric hemorrhages. Chronic anemia was a prominent finding and was attributed to chronic blood loss from repeated epistaxis and hematemesis. The pulmonary arteriovenous aneurysm was demonstrated by the method of angiocardiography to be located in the left lower lobe, adjacent to and partially overlying the cardiac apex. Confusing auscultatory findings were present and were difficult clinically to distinguish from those of intrinsic cardiac valvular disease. Spleen and liver were palpable. Cyanosis and polycythemia were apparently obscured by blood loss anemia but both appeared after a hemorrhage-free period. Arterial blood oxygen saturation was reduced.

In the second case there were telangiectases present on the skin of the hands, face and feet as well as on the buccal and nasal mucous membranes. The arteriovenous aneurysm was demonstrated by angiocardiography to lie in the posterior portion of the apex of the right lower lobe. She was cyanotic with early clubbing of the fingers although definite polycythemia with increased blood volume was not substantiated by laboratory studies. Arterial blood oxygen saturation was, however, reduced.

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Congenital Hypoprothrombinemia*

A Case Study with Particular Reference to the Role of Non-prothrombin Factors in the Conversion of Prothrombin

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THE importance of non-prothrombin plasma factors in the velocity of prothrombin conversion to thrombin has been established recently.[1–4] The one-stage method for prothrombin determination is based upon the time required after the addition of optimal thromboplastin and calcium for the evolution of enough thrombin to clot the fibrinogen in plasma. This value depends upon the concentration not only of prothrombin but also of non-prothrombin plasma factors.[5] Owren[1] reported on a patient with hemorrhagic phenomena referable to deficiency of a hitherto undescribed plasma component important in prothrombin conversion. The prothrombin time was markedly elevated despite the fact that the prothrombin concentration was normal. Cases with similar deficiencies have been reported by Quick.[6]

The term "idiopathic hypoprothrombinemia" has been applied to numerous cases characterized by a prolonged one-stage prothrombin time, resistance to vitamin K therapy and control of hemorrhage with infusion of normal whole blood or plasma.[7–10] In most instances, however, it is not clear whether the disturbance was due to a deficiency of prothrombin or to non-prothrombin factors. The use of the term "hypoprothrombinemia" in these cases may, therefore, not be justified.

It is the purpose of this paper to present observations on a five week old child with true prothrombin deficiency.† His plasma proved particularly valuable in providing additional information on the importance of non-prothrombin factors in the velocity of thrombin evolution from prothrombin.

CASE REPORT

E., a five week old male infant, was admitted to the Children's Hospital on October 24, 1948, with rectal bleeding. The parents were first cousins and had no Rh incompatibility. A child, born to them four years earlier, died eight days after birth, severely jaundiced and bleeding from the gastrointestinal tract. The diagnosis was hemorrhagic disease of the newborn. By a previous marriage the father had had a son whose two children had congenital defects, one hypospadias, and the other, congenital heart disease.

The patient was a full term infant, born after normal delivery, and weighed 7 pounds 6 ounces. During the first day there was minimal cyanosis of hands and feet and on the fourth day slight icterus. He gained weight and was discharged on the seventh day. Thereafter the child became pale and irritable and refused feedings. He developed subnormal temperature and rapidly went into shock.

At three weeks he was readmitted because of blood and mucus in the stool. Hemoglobin was 34 per cent of normal, red blood cells 2.77, white blood cells 18,000, differential normal. The

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bleeding time was one and one-half minutes, clotting time two and one-half minutes, the platelet count 230,000. The stool contained 4+ occult blood. Spinal fluid was xanthochromic and under normal pressure. Small intraperitoneal transfusions caused improvement until the eleventh hospital day when he again became irritable and passed bloody stools. Because he was thought to have bilateral otitis media, his ears were lanced and yielded a serosanguineous discharge. A diagnosis of generalized sepsis was made. The patient had received 4.8 mg. of vitamin K intramuscularly every six hours for two days without effect.

On admission to the Children's Hospital the patient appeared sallow and pale. Physical examination was negative except for a barely palpable liver. The hemoglobin was 9 gm. per 100 cc. of blood; red blood cells 3.54, white blood cells 14,000. The bleeding time was four and one-half minutes, clotting time two minutes; clot retraction was good. The stools contained occult blood. Proctoscopic examination was negative. A barium enema revealed no remarkable findings.

An exploratory laporatomy and incidental appendectomy were done. The liver, spleen and kidneys appeared normal and no source of the gastrointestinal bleeding was found.

The patient continued to have bloody stools. The prothrombin time was forty seconds (normal control twelve seconds). Another bleeding time was four and three-fourths minutes; the clotting time (Lee and White) twelve minutes. One week later the prothrombin time was sixty seconds and the platelet count 280,000. The plasma fibrinogen concentration was normal. Several intraperitoneal blood transfusions, intramuscular vitamin K and Fraction I (Harvard) had no effect on the hemorrhagic condition.

Five weeks after admission the child received 100 cc. of normal, fresh, citrated plasma intravenously. The donor had 100 per cent prothrombic activity. The patient's prothrombic activity rose promptly from 2 to 50 per cent. It fell rapidly until, twelve hours later, it had returned to its original value. (Fig. 2.)

Four days later the patient was discharged. On the following day he began to vomit and developed pallor. His stools again showed occult blood. He became irritable, had several convulsions and died four days after leaving the hospital. Autopsy was not performed.

METHODS

Plasma prothrombic activity was measured by both the orthodox method of Quick[11] and the modification of Rosenfield and Tuft[5,12] in which prothrombin free normal plasma is used as diluent. Serum prothrombic activity and prothrombin conversion accelerator (spca) were determined by the method of deVries, Alexander and Goldstein.[13]

RESULTS

The prothrombin time (Quick) of the child was seventy-six seconds corresponding to a prothrombic activity 1 to 2 per cent of normal. The clotting time was normal. The serum, obtained one hour after coagulation, oxalated, and incubated one-half hour at 37°C. was devoid of prothrombic activity. No appreciable spca could be demonstrated.

Whether the prolonged prothrombin time was due to low concentration of prothrombin and/or to inadequacy of non-prothrombin factors remained to be established. Ideally this could be done by the addition to the patient's plasma of plasma free of prothrombin but normal in all other respects. Experiments were run in which normal plasma was treated with $BaSO_4$ according to the technic of Rosenfield and Tuft.[13] The prothrombin-free normal plasma was then mixed with the patient's plasma in the proportion of 2:1. The mixture showed no greater prothrombic activity than could be attributed to the small amount of prothrombin present in the patient's plasma. (Table 1.) This would indicate that the patient suffered from an actual deficiency of prothrombin.

The question arises whether the patient also had a defect in non-prothrombin factors. The following experiments were done: the patient's plasma was treated with $BaSO_4$ and then used as diluent for normal plasma. The prothrombic activity of the mixtures was no different from that of normal plasma similarly diluted with normal $BaSO_4$ plasma. (Table 1.) Since the patient's $BaSO_4$ plasma was indistinguishable from

normal $BaSO_4$ plasma in its effect on the velocity of prothrombin conversion, it may be concluded that the patient's plasma was normal in non-prothrombin factors important in the conversion of prothrombin to thrombin.

TABLE I
PROTHROMBIC ACTIVITY (ONE-STAGE) OF NORMAL AND PATIENT'S PLASMA IN VARIOUS COMBINATIONS WITH NORMAL PLASMA, NORMAL $BaSO_4$ PLASMA AND PATIENT'S $BaSO_4$ PLASMA

Plasma Mixture (Parts)				Prothrombin	
Patient's Plasma	Normal Plasma	Normal $BaSO_4$ Plasma	Patient's $BaSO_4$ Plasma	Time (Seconds)	Activity (Per cent)*
1	..	..	..	70.0	2.5
1	..	2	..	89.0	3.0
..	1	9	..	26.0	120
..	1	..	9	27.2	112
9	1	..	..	19.5	270
19	1	..	..	23.4	320
29	1	..	..	25.0	390
39	1	..	..	31.8	328

* On basis of normal plasma containing 100 per cent prothrombin. All values are corrected for dilution with diluting plasma and were obtained by interpolation from standardization curve for normal plasma diluted with normal $BaSO_4$ plasma. (Fig. 1.)

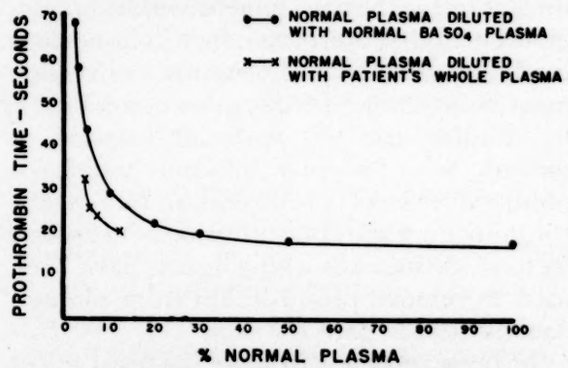

FIG. 1. Relation between prothrombin time and prothrombin concentration of mixtures of normal plasma with (1) $BaSO_4$ normal (prothrombin-free) plasma or (2) patient's hypoprothrombinemic plasma.

This conclusion is based upon the assumption that adsorption with $BaSO_4$ does not affect the concentration of these accessory factors. If this assumption is correct, the patient's whole plasma, containing negligible quantities of prothrombin, should be indistinguishable from his $BaSO_4$ plasma as a diluent for normal plasma. Accordingly, normal plasma was diluted in various proportions with the patient's whole plasma. The prothrombic activities of these mixtures were consistently *higher* than the prothrombic

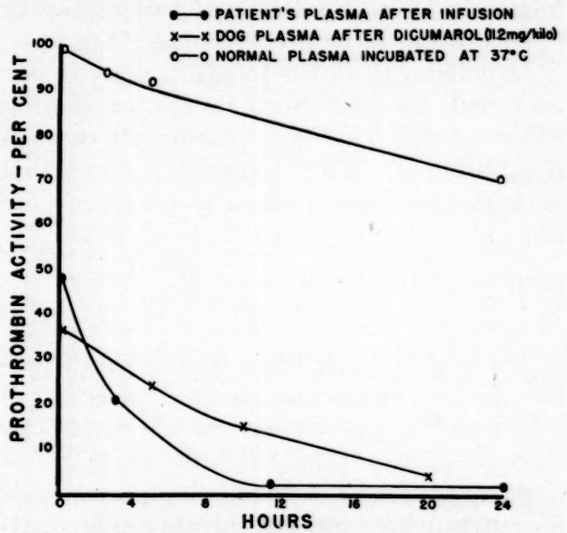

FIG. 2. Relative rates of disappearance of prothrombic activity from (1) patient's blood after plasma infusion, (2) human plasma *in vitro* and (3) dog blood after dicumarolization. Only those observations in the dog are recorded which are below 40 per cent prothrombic activity in order to make the curve of "decay" more comparable to that in the patient whose prothrombic activity immediately after infusion was 50 per cent of normal.

activities of normal plasma similarly diluted with the patient's $BaSO_4$ plasma or with $BaSO_4$ normal plasma. (Table I, Fig. 1.) This discrepancy between the effect of the patient's whole plasma and his $BaSO_4$ plasma on the velocity of prothrombin conversion indicates that $BaSO_4$ removed some prothrombin conversion accessory factor from the patient's plasma, and that the original assumption was not correct in this patient.

The evidence thus far shows that the patient had hypoprothrombinemia. The administration of prothrombin in normal plasma should rectify this defect; 100 cc. of fresh normal citrated plasma were administered intravenously. The prothrombic activity of the donor's plasma was approximately 100 per cent. The activity of the patient's plasma was determined at specified

intervals following the infusion. (Fig. 2.) The rate of disappearance of the prothrombic activity from the patient's blood was faster than that observed in a dog given large doses of Dicumarol. Normal plasma, however, when incubated at body temperature for twenty-five hours showed a much slower deterioration in its prothrombin. (Fig. 2.)

Deficiency in anti-hemophilic activity was excluded by the normal clot-promoting effect of the patient's plasma on known hemophiliacs. The plasma prothrombic activities of the patient's parents were normal.

COMMENT

The recent recognition of non-prothrombin factors important in the velocity of prothrombin conversion to thrombin by thromboplastin plus calcium raises questions regarding the specificity of methods for measuring plasma prothrombin. Although many cases of "idiopathic hypoprothrombinemia" have been reported, a re-evaluation of the data in the light of this recent knowledge raises doubt whether the defect in these cases resided in a deficiency of prothrombin or of non-prothrombin factors. Clearly the orthodox one-stage method of Quick measures over-all velocity of thrombin evolution and cannot differentiate between retardation due to low prothrombin concentration and that due to inadequacy of accessory factors. Therefore, before a diagnosis of hypoprothrombinemia can be made by the one-stage technic, deficiencies of the accessory factors must be excluded.

In the case herein reported the deficiency is clearly prothrombin. This was demonstrated by the following: (1) providing the patient's plasma with prothrombin-free normal plasma ($BaSO_4$ plasma) did not increase the prothrombic activity; (2) the patient's $BaSO_4$ plasma was indistinguishable from normal $BaSO_4$ plasma in its effect on the velocity of thrombin evolution in normal plasma. This indicates that the patient's plasma contained all of the non-prothrombin factors present in $BaSO_4$ normal plasma.

The hypoprothrombinemia was probably congenital (perhaps familial) in origin in view of the onset of hemorrhage shortly after birth, history of hemorrhage in an infant brother, resistance to vitamin K therapy and other congenital defects in second cousins.

The observation that a small amount of normal plasma mixed with the patient's plasma gave a faster prothrombin time (higher prothrombic activity) than a mixture of the same normal plasma with $BaSO_4$ normal plasma or with $BaSO_4$ patient's plasma indicates that the $BaSO_4$ removed a non-prothrombin accessory moiety from the patient's plasma. Whether this factor is present to the same degree in normal plasma and is likewise removed by $BaSO_4$ remains to be elucidated. It is conceivable that the faster conversion of prothrombin in the patient's whole plasma may be due to greater concentrations of accessory factors in the patient's plasma or, less likely, to the presence of an additional accessory agent. This might reflect a physiologic compensation for prothrombin deficiency.

In the specific determination of prothrombin by the one-stage procedure, adequacy of non-prothrombin factors important in the velocity of prothrombin conversion must be assured.[5] Ideally, this can be done by diluting the test material (plasma or serum) with normal plasma which is rendered free of prothrombin but which contains a normal concentration of accessory factors. Various adsorbing agents have been used to remove prothrombin from plasma. Among these $BaSO_4$[14] and $Ca_3(PO_4)_2$[15] have been reported to have the least effect on prothrombin accessory factors. Owren,[1] however, found that substantial amounts of Factor v are removed by $BaSO_4$ although the exact amount used is not clear. Our data indicate that this adsorbing agent removed some accessory factor or factors from the patient's plasma. It is probable that normal plasma is similarly affected. $BaSO_4$ does not remove Labile Factor[14,15] since $BaSO_4$ nor-

mal plasma is fully capable of rectifying the retarded prothrombin conversion of aged plasma. It is, therefore, likely that $BaSO_4$ removes another accessory factor, perhaps Factor v of Owren. On the basis of this hypothesis two accessory prothrombin factors exist in normal plasma: one, the Labile Factor, and the other, a substance adsorbed by $BaSO_4$. Accordingly, $BaSO_4$ plasma may not be ideal as a diluent in one-stage prothrombin methods.

The rate of disappearance of injected prothrombin from the patient's plasma is of both academic and clinical interest. Since *in vitro* the deterioration of prothrombin in plasma is much slower, utilization or active destruction of the administered prothrombin must have occurred in the patient. This suggests that under normal conditions prothrombin may similarly be consumed and regenerated rapidly. That it disappeared faster in the patient than in heavily dicumarolized dogs raises the question of the existence of prothrombin stores in a normal individual which can be called upon when prothrombin synthesis is blocked in the liver.

The rapid disappearance of the infused prothrombin indicates that frequent transfusions with normal blood, plasma or prothrombin fractions would have been required to maintain a clinically effective level of circulating prothrombin.

CONCLUSIONS

1. A case of true hypoprothrombinemia, probably congenital, is reported.

2. Accessory factors important in the velocity of thrombin evolution were either normal or in excess.

3. Observations on the rate of disappearance of administered prothrombin are given.

4. $BaSO_4$ removed a non-prothrombin plasma constituent important in prothrombin conversion. Its possible identity with Factor v of Owren is suggested.

5. Limitations of the one-stage method in the determination of prothrombin are discussed.

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The Demonstration of Antibody in Acute Hemolytic Anemia Complicating Infectious Mononucleosis*

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THE development of acute hemolytic anemia during the course of infectious mononucleosis has only recently been reported.[1-3] Dameshek and Schwartz[4] had previously reported the occurrence of hemolytic anemia in a patient with infectious mononucleosis but sulfadiazine had been administered. Serologic tests for the presence of autohemagglutinins and hemolysins were made in two of these reports. Ellis, Wollenman and Stetson[1] described the occurrence of acute hemolytic anemia in an illness resembling infectious mononucleosis in which autohemagglutinins, hemolysins and a positive Donath-Landsteiner test were found. In their case the heterophile antibody titer was markedly elevated initially as were the hemagglutinin titers. Coincident with the fall in the heterophile antibody titer a decrease in serum hemagglutinins was demonstrated. Appleman and Morrison[2] reported an instance of acute hemolytic anemia concomitant with infectious mononucleosis. They were unable to demonstrate hemagglutinins or hemolysins in the patient's serum.

In the case herein described hemagglutinins and hemolysins were not noted except as demonstrated by the Coombs (antihuman precipitin serum) reaction[5] which was found to be positive during the hemolytic phase of the disease and which has since become negative.

CASE REPORT

G. P., a seventeen year old negress, was admitted to Queens General Hospital on October 2, 1948, because of jaundice. Her illness began one week before with anorexia, nausea, vomiting and malaise followed by dull, steady, non-radiating epigastric distress. The urine was noted to have become dark in color but the stool was normal. Preceding respiratory infection was denied. The use of drugs prior to admission was also denied. The past history and family history were non-contributory.

Physical examination revealed a young negro girl who was acutely ill. Her blood pressure was 110/50, her temperature 102°F. Examination of her head showed nothing abnormal. The conjunctivas and mucous membranes were pale. The scleras were icteric. The eyes were otherwise normal. The pharynx was mildly injected. The neck was supple. The anterior and posterior cervical glands were moderately enlarged. The axillary and inguinal nodes were also significantly increased in size. The lungs were clear. The heart was not enlarged and the rate was regular. A systolic murmur was heard over the entire precordium, maximally at the aortic area. The spleen was palpable one finger below the costal margin and the liver was enlarged to two fingerbreadths below the costal margin. Right costovertebral angle tenderness was noted. No other masses were present. Neurologic examination was normal.

Laboratory examination on admission revealed the following: hemoglobin, 8 gm. per cent, white blood cells 10,000 per cu. mm., 66 per cent of which were lymphocytes. Many of these lymphocytes were atypical and characteristic of infectious mononucleosis.[7] The red cells were hypochromic with only occasional spherocytes. Sickle-cell preparations were negative. The urine was normal except for increased urobilinogen to a dilution of $\frac{1}{80}$. Blood serology revealed a doubtful positive Wassermann and

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the Mazzini test was 2 plus positive. The heterophile agglutination test was positive only to a dilution of 1/64. The blood sugar was 106 mg. per cent and the blood urea nitrogen was 9 mg. per cent. The total protein concentration was 7.8 gm. per cent, albumin 4.6 and globulin 3.2. The total cholesterol was 160 mg. per cent. The prothrombin time was 80 per cent of normal and the alkaline phosphatase 4.5 King-Armstrong units. The electrocardiogram and a chest x-ray were both negative.

For the first week the patient was febrile ranging from 101° to 102°F. The temperature then fell slowly and was normal by the tenth hospital day. Pharyngitis was most marked for the first three days and the cervical adenopathy was greatest at this time. The jaundice, too, was most pronounced during this period but rapidly subsided thereafter. The remaining clinical course was completely uneventful.

On the third hospital day the hemoglobin concentration had fallen to 5.5 gm. per cent and the erythrocyte level to 2.01 million cells per cu. mm. About 20 per cent of the red cells were spherocytic. There were 11,350 white cells per cu. mm. with many atypical lymphocytes noted. Two normoblasts per 100 white cells were present in the peripheral blood. A reticulocytosis of 10.7 per cent was recorded. The urinary urinobilinogen persisted at a dilution of 1/80. On the tenth hospital day the patient had improved considerably. A continuing reticulocyte response of 6.4 per cent was present. The hemoglobin concentration had spontaneously risen to 9.0 gm. per cent. The urinary urobilinogen level had fallen to 1/40. Cephalin flocculation was three plus in twenty-four and forty-eight hours and the alkaline phosphatase had risen to 7.0 units. The icterus index was five at this time. Heterophile agglutination titer was now positive to 1/512 dilution. Repeated sickling preparations were negative. Bleeding, clotting and clot retraction times were normal. A saline cell fragility test was normal. Bone-marrow aspiration disclosed a total nucleated cell count of 200,000 cells per cu. mm. with thirty-five megakaryocytes per counting chamber. There were myeloblasts 1 per cent, neutrophilic myelocytes 13.0 per cent, neutrophilic non-segmented forms 18.3 per cent, segmented forms 15.3 per cent, eosinophilic myelocytes 0.3 per cent, eosinophilic non-segmented forms 0.7 per cent, basophilic segmented forms 0.3 per cent, lymphocytes 3.7 per cent, monocytes 2 per cent, reticuloendothelial cells 1 per cent, plasma cells 0.3 per cent, megakaryocytes 0.3 per cent, pro-erythroblasts 1 per cent, erythroblasts 6 per cent and normoblasts 39.3 per cent. Tests for serum isoagglutinins at 37°C. and at 4°C. were negative. A modification of the Donath-Landsteiner test for hemolysins was negative. The Coombs test of the patient's washed red cells was 4 plus positive.

The subsequent clinical course and convalescence was uneventful. The jaundice disappeared. The spleen and lymph nodes became reduced in size. The hemoglobin concentration continued to rise and on the twenty-fourth hospital day, the day of discharge, 12.5 gm. per cent hemoglobin and 4.38 million erythrocytes were found. The white blood cell count stabilized at a level of 7,000 cells per cu. mm. and the differential pattern assumed normal proportions. The urine was completely normal. The cephalin-flocculation test was negative. The Wassermann and Mazzini tests were now repeatedly negative. The heterophile agglutination titer continued to be positive in high dilution and was 1/512 the second week of hospitalization and 1/128 on discharge. Auto-agglutinins and hemolysins could not be demonstrated in the serum but the Coombs precipitin test continued to be strongly positive on discharge.

The patient was next seen in the hematology clinic eleven weeks after discharge. She felt well in the interim. The cervical lymph nodes were still slightly enlarged. The liver and spleen were not palpable. The hemoglobin was 12.0 gm. per cent red blood cells 5.2 million per cu. mm. and white blood cells 7,900 per cu. mm. The differential study was normal. The heterophile agglutination titer was positive only to 1/64 and the Coombs precipitin test was negative.

The patient was completely asymptomatic when last seen fifteen weeks after discharge and nineteen weeks from the onset of her illness. The cervical nodes, liver and spleen were not enlarged. The hemogram was almost identical with that of the previous month. Heterophile agglutination titer was still 1/64 and the Coombs precipitin test was again negative.

COMMENTS

A simple method for the specific detection of antibodies in serum or plasma was described by Coombs, Mourant and Race in 1945. The reagent is an antihuman precipitin serum which reacts only with those red cells having absorbed a human serum

fraction on to their surface. These cells are therefore said to be coated. The serum fraction involved is presumed to be an immune globulin in the form of an incomplete antibody. This phenomenon is thought to be immediately related to the hemolysis in acquired hemolytic disease. Why autosensitization of red cells occurs is not understood.

In the case presented the Coombs test was strongly positive during the hemolytic crisis and remained positive even when all signs of hemolytic disease were long absent. Two months after discharge the Coombs test was found to be negative. Five patients with infectious mononucleosis and heterophile antibody titers of magnitudes similar to those observed in this patient were tested with the Coombs reagent. In all, the Coombs test was negative throughout their hospital stay. Two of these patients had jaundice and a mild hepatitis.

We found no demonstrable auto-agglutinin in the serum of our patient when tested against saline and albumin suspensions of group-compatible red cells of five subjects. The red cells of two of these subjects were incubated with the patient's serum at 37°C. for twelve hours. The red cells were then washed thoroughly with fresh saline and tested with the Coombs reagent. In each of the two experiments the Coombs test was positive, demonstrating the presence of otherwise non-demonstrable serum antibody.

SUMMARY

A case of acute hemolytic anemia and infectious mononucleosis in a seventeen year old negress is presented. By the use of the Coombs reagent autosensitization of the patient's red cells was demonstrable during the hemolytic phase of the disease.

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Aerosol Penicillin in the Treatment of Chronic Lung Abscess*

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PRIOR to the use of antibiotic therapy in the treatment of lung abscess, surgical drainage or extirpation was the treatment of choice with a reported mortality in excess of 10 per cent.[1] Although many abscesses probably resolve spontaneously without clinical recognition or treatment, the chance of spontaneous healing is slight when a definite diagnosis can be established. Under the best conservative methods of management more than half of the acute lung abscesses become chronic.

The use of sulfonamides proved disappointing except in certain isolated cases in which a susceptible organism in pure culture was obtained by bronchoscopic aspiration. The remarkable success of penicillin therapy in pneumonia and empyema[2] led to its trial in chronic suppurative diseases of the lungs. In a study by Kay and Meade seventeen patients with chronic lung abscess were treated with intramuscular penicillin. While the group as a whole showed some decrease in toxicity as reflected in a fall in pulse and temperature and lessening of the cough and sputa with a decrease in the surrounding pneumonitis, only one patient healed completely. Surgical drainage eventually was employed in the other sixteen. In addition it was noted that the bacterial flora was not appreciably affected. Intratracheal penicillin was employed in several patients with bronchiectasis and chronic bronchitis, and it was observed that this method of administration appeared to be of greater benefit than the intramuscular route.

Smyth and Billingslea[4] collected a series of thirty-one patients with lung abscess treated with intramuscular penicillin and added four of their own. Of the thirty-five cases twelve were reported as acute lung abscess, four as chronic lung abscess; the duration of the remaining nineteen was not reported. The individual dosage schedules were variable with the total amount of penicillin administered ranging between 600,000 and 6,300,000 units. Sixteen were reported as cured, nine improved and ten were not benefited.

The topical application of penicillin to the tracheobronchial passageways by inhalation of an aerosol has been employed by some investigators in the treatment of bronchopulmonary infection.[5,6] A review of the literature revealed a total of eighteen patients with lung abscess treated with aerosol penicillin, of whom eleven had acute lung abscess while the remaining seven had chronic lung abscesses. Barach et al.[5] reported six cases of lung abscess of which two were acute and four chronic. Three of the patients were benefited markedly. Of the three cases showing no improvement two were patients with long-standing bronchiectasis and chronic abscesses. Segal and Ryder[7] reported four patients treated with 25,000 units of penicillin aerosol every three hours. Their first two patients were treated preoperatively. A third patient was entirely cured after six weeks of therapy and a fourth with multiple pulmonary infarcts and a lung abscess improved slowly

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but completely. Garthwaite and Barach gave seven courses of penicillin aerosol therapy to five patients with acute lung abscess. They reported marked improvement in four, slight improvement in two and no improvement in one. Of three patients with chronic lung abscess two showed marked benefit while one showed no change. The daily dosage of penicillin employed varied between 150,000 and 500,000 units, generally given as three to five inhalations

The medical management of lung abscess with penicillin aerosol presents a new approach to this disease. Because the number of reported cases so treated have been few the authors are presenting a patient with lung abscess who responded favorably under such medical management.

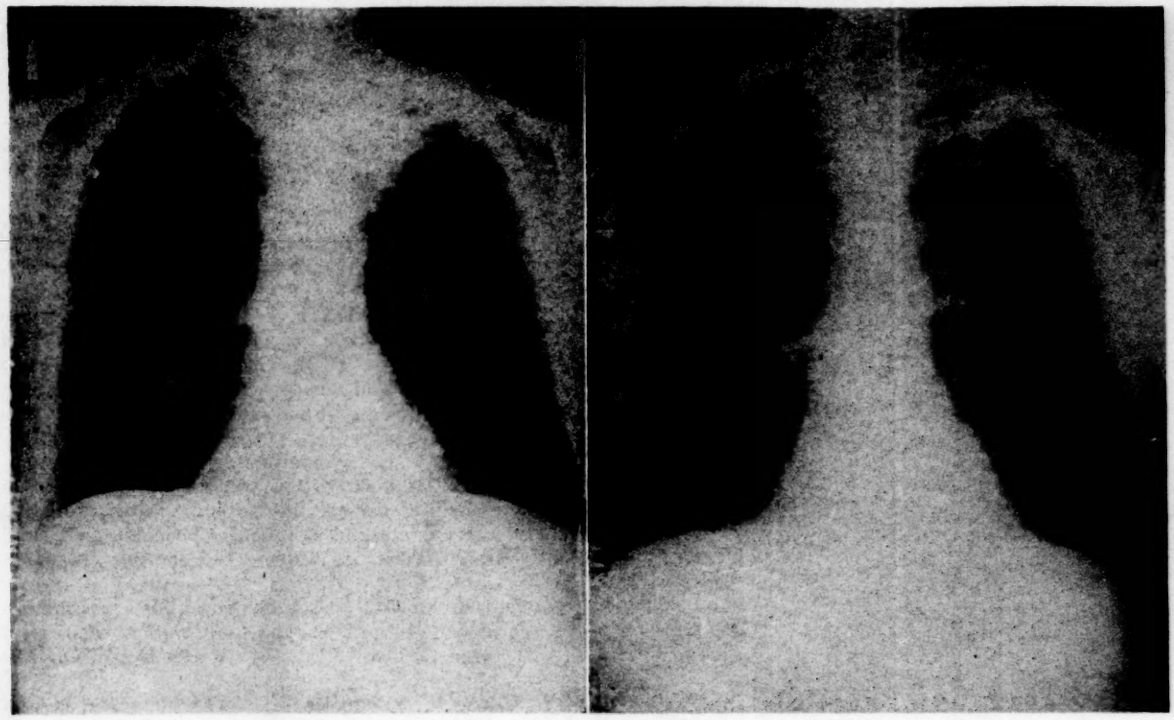
CASE REPORT

F. F., a sixty-seven year old white man, was admitted from another hospital to the Goldwater Memorial Hospital on November 14, 1947, with a diagnosis of malnutrition and chronic bronchitis. For the past ten years the patient had had a chronic cough productive of approximately 1 ounce of mucoid sputum daily unassociated with loss of weight, febrile episodes or night sweats. About six months prior to admission, while in apparent good health, the cough became more frequent and he began to notice some weight loss. Because of marked asthenia associated with an acute episode of diarrhea he was hospitalized on November 5, 1947. During the stay at this institution a low-grade febrile course was noted and he was transferred for further study. The past history revealed poor dietary intake with approximately 1 pint of whiskey consumed daily.

The initial physical examination disclosed a thin, undernourished male with a temperature of 100°F. and blood pressure of 120/60. Cardiac examination was negative. Weight on admission was 147 pounds (6 months ago, 175 pounds). The positive findings were limited to the respiratory system. The diaphragm moved freely with respiration. Tactile fremitus was diminished over the left apex posteriorly with hyperresonance in the same region. Amphoric breath sounds were present over the left apical region both anteriorly and posteriorly. The urine was negative. The blood count showed 11,000 white blood cells with 88 per cent polymorphonuclears showing toxic granulation; 4,000,000 red blood cells with 9.5 gm. hemoglobin; ESR 50 mm./hr., hematocrit 38. The urea nitrogen, total protein, A/G and cholesterol were normal. The ECG tracing showed a slight tachycardia but otherwise was within normal limits. Chest x-ray on November 17, 1947, revealed an opacity in the left upper lung field with an area of radiolucency in the center and a fluid level. There was emphysema of the remaining lung. The heart and mediastinum were displaced slightly to the right. Impression: Cavitation of left upper lobe with fluid level.

The patient ran a low-grade febrile course with temperatures ranging between 100 and 101.5°F. Cough was productive of approximately 4 ounces of mucopurulent, foul-smelling sputa daily. Repeated smears and cultures were negative for tubercle bacillus and a guinea pig inoculation was also negative. The tuberculin skin test was positive in 1:10,000 dilution. A culture of the sputum on December 5, 1947, revealed gram-positive cocci predominating with Staphylococcus aureus hemolyticus, pneumococci and Streptococcus viridans isolated. For a period of almost one month, November 17th through December 12, 1947, he was given intramuscular penicillin 30,000 units every three hours for a total dosage of 6 million units combined with several courses of sulfadiazine therapy. The chest x-ray on December 1st showed no change and when repeated twenty-five days later, the air content of the cavity appeared to be increased. (Fig. 1.) On bronchoscopy the left upper lobe bronchus was visualized but no drainage or disease was noted. A bronchogram performed at this time visualized the left bronchial tree except for the apical and subapical regions. There was no evidence of dilatation.

On February 6, 1948, penicillin aerosol inhalations, 100,000 units five times daily, were administered by the mask inhalation technic employing a demand valve.[9] After ten days of therapy the patient became afebrile and the sputa diminished to less than ½ ounce daily. A chest x-ray on February 27th showed productive changes in the left apex but the abscess cavity previously visualized was not evident. (Fig. 2.) Repeated cultures of the sputa revealed only gram-negative Bacillus aerogenes. The penicillin inhalations were discontinued on March 16th and a chest film two days later showed



1 2

FIG. 1. Chest film taken December 26, 1947, after a course of intensive penicillin therapy intramuscularly; cavity with fluid level in the left subapical region.

FIG. 2. Film taken February 27, 1948, following three weeks of penicillin serosol inhalation; productive changes are present at site of former abscess; residual lipiodol present in lower lung fields and hilar regions.

further clearing. On routine care including a high protein, high caloric diet, the patient gained 20 pounds in body weight. He remained asymptomatic and a repeat bronchoscopy on May 12th was negative. A culture of the aspirated bronchial secretion was sterile. A follow-up chest film at this time showed only slight residual scarring at the left apex. (Fig. 3.) The patient was discharged on July 14, 1948, eight months after admission.

COMMENT

The interesting feature of this report was the therapeutic response to aerosol penicillin after adequate trial by the intramuscular route had failed. In a preliminary report by Barach et al.[5] two cases of lung abscess were included in which penicillin had been previously given for one month by intramuscular injection without significant effect. Administration of penicillin aerosol was followed by recovery. Following inhalation of penicillin and streptomycin mists exceptionally high sputum levels were obtained in contrast to the zero levels generally present after intramuscular administration.[10] It was believed that the poor result with parenteral penicillin may have been due to a failure to arrest bacterial growth on a bronchial surface lined with purulent exudate. In addition we may speculate that the capillary blood supply in and about the cavity was impaired and hence affected the distribution of the antibiotic to the diseased portion of the left upper lobe via the circulation. Bobrowitz[11] and other investigators[12,13] have subsequently confirmed the value of penicillin aerosol in chronic pulmonary suppuration and demonstrated that the maintenance of a high penicillin level locally in the bronchial secretions was more effective therapeutically especially in those instances of bronchopulmonary infection due to the more highly resistant organisms, notably Staphylococcus aureus and Friedländer's bacillus.

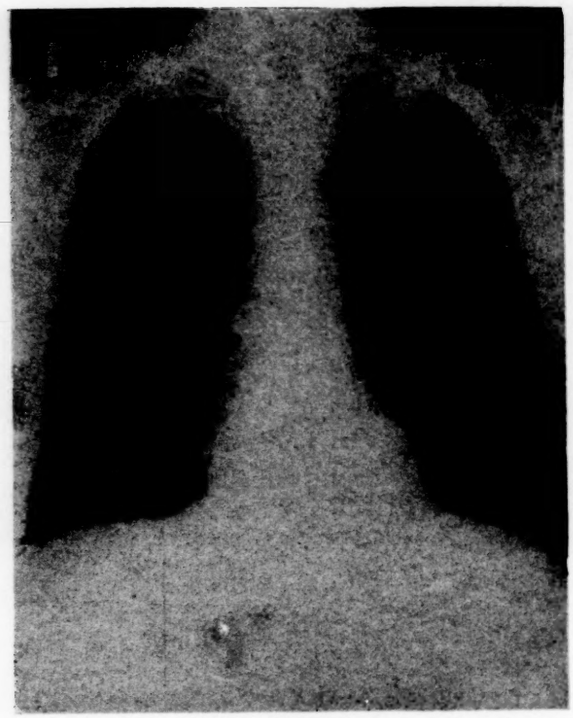


FIG. 3. Film dated May 12, 1948, two months following completion of aerosol therapy, revealed slight residual scarring at the left apex.

SUMMARY

1. A case of chronic lung abscess of the left upper lobe is presented. Complete recovery occurred with penicillin inhalation therapy. Previous intensive chemotherapy and intramuscular penicillin had failed to effect the course of the disease.

2. The application of topical therapy through deposition of penicillin aerosol upon a diseased segment of the bronchopulmonary tree proved singularly effective in this instance and may constitute an important addition to the medical management of lung abscess.

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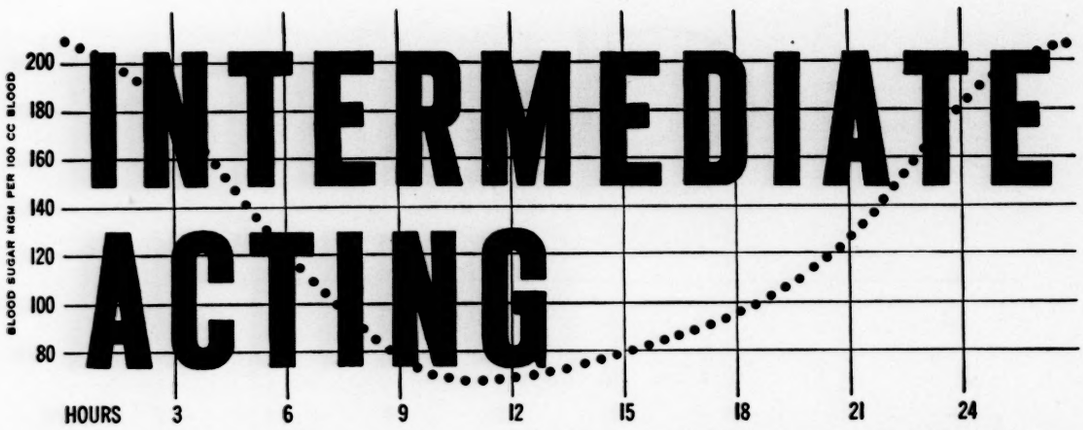

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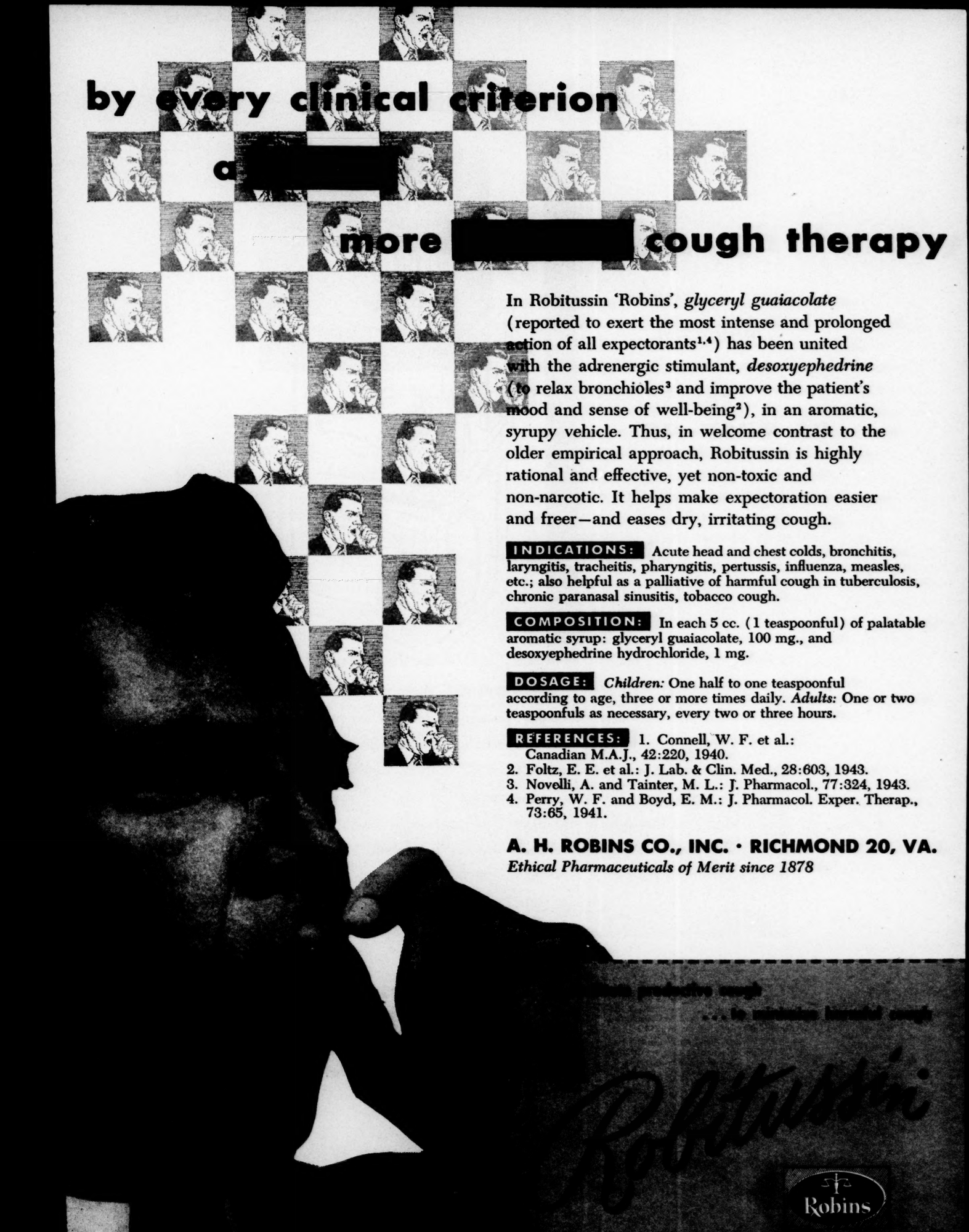

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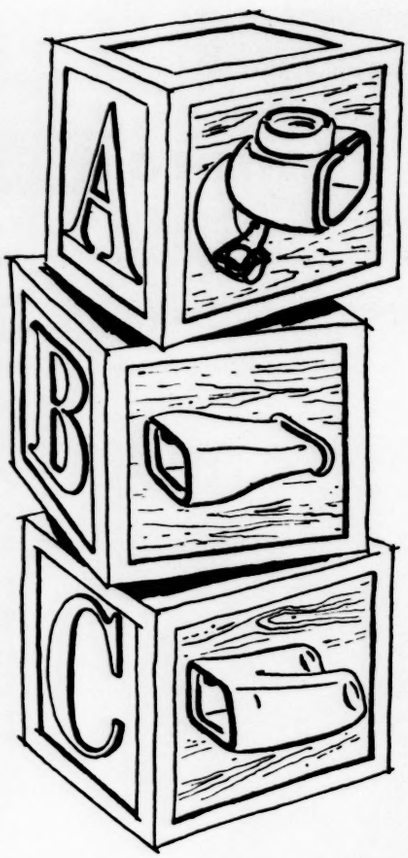

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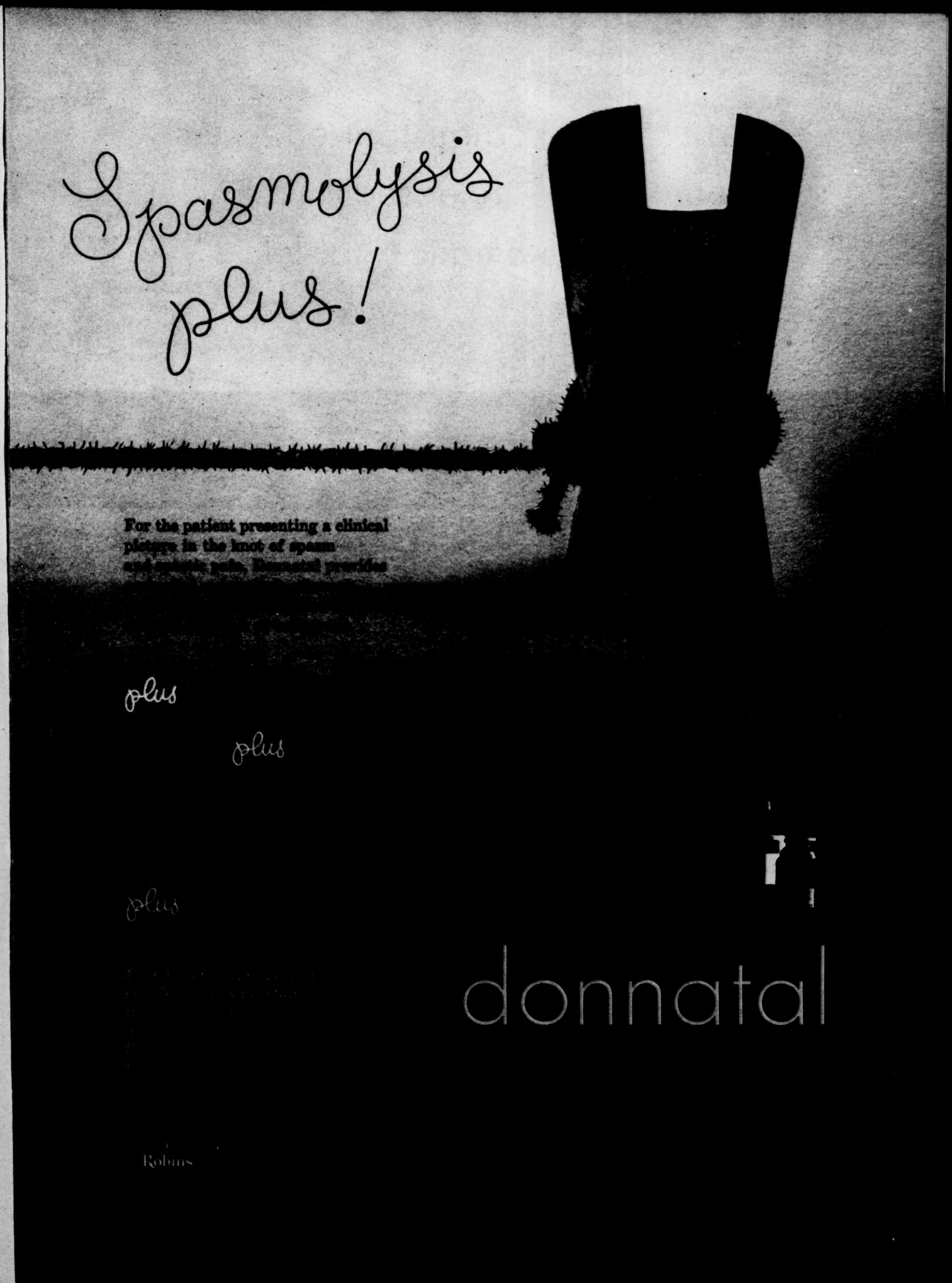
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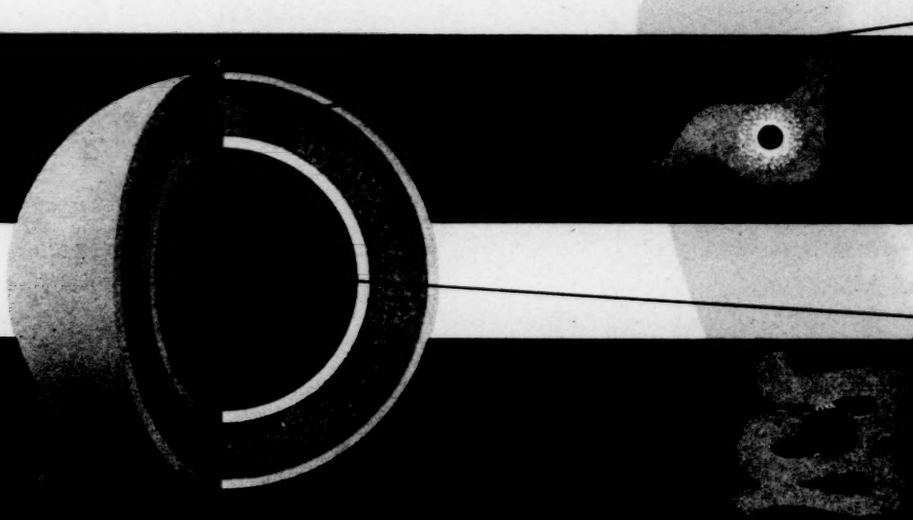

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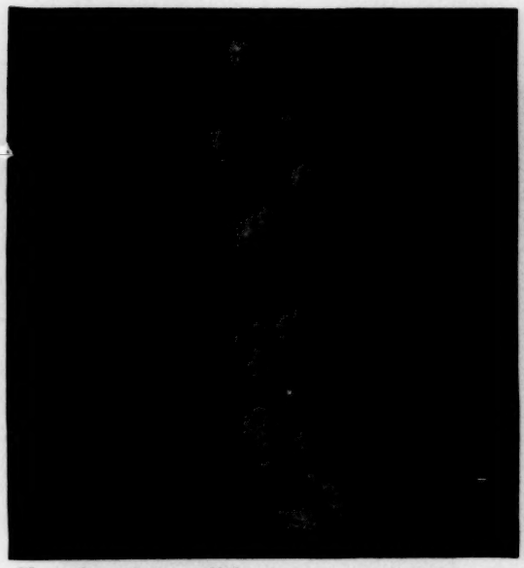

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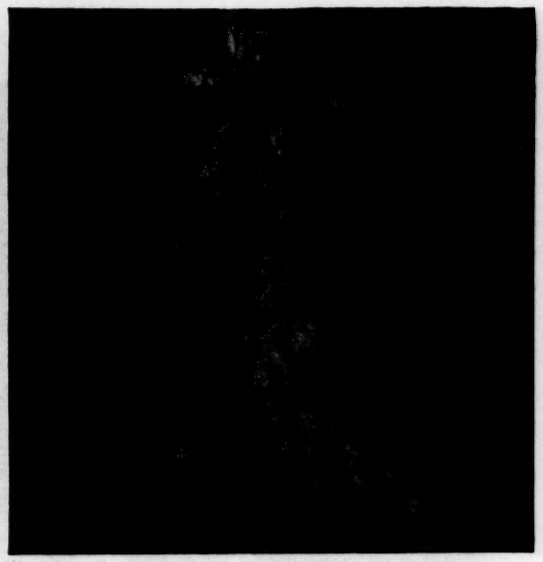

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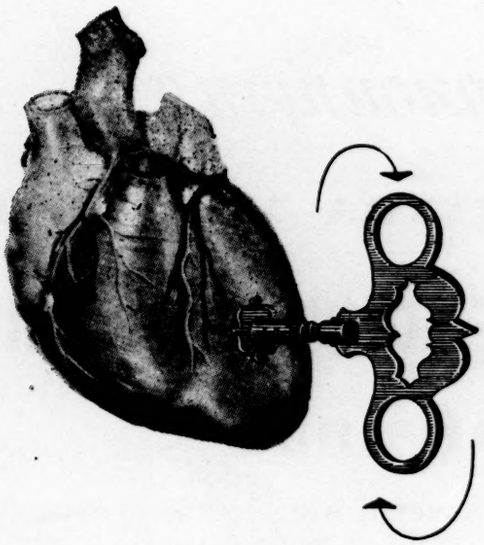

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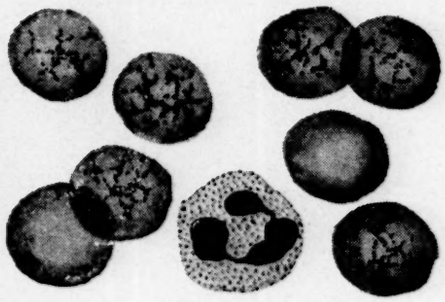

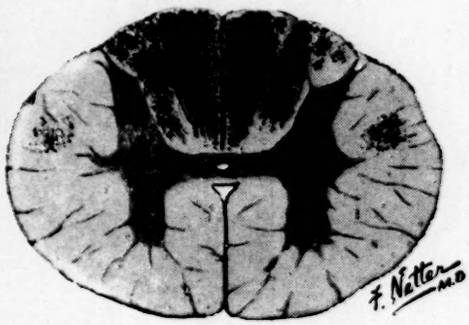

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